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Case Report

Treatment of Severe Hypertriglyceridemia During Pregnancy With High Doses of Omega-3 Fatty Acid and Plasmapheresis

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Abstract

Objective: Severe hypertriglyceridemia carries increased health risks, including the development of pancreatitis. The objective of this study was to report on management of 2 cases with severe gestational hypertriglyceridemia.

Cases: In case 1, a 33-year-old pregnant woman presented with serum triglyceride level of 14 000 mg/dL after discontinuing hypolipidemic medications. She was treated with Lovaza 12 g/day, and serum triglyceride remained near normal at level of less than 800 mg/mg/dL until delivery. In case 2, a 28-year-old patient (29th week gestation) presented with acute pancreatitis and triglycerides >4000 mg/dL. She was treated with Gemfibrozil, Lovaza, insulin infusion, subcutaneous heparin, and escalated to plasmapheresis. She successfully delivered a baby at the week of 36th and her triglyceride level was 304 mg/dL after that.

Discussion: Case 1 was treated with high-dose Lovaza and case 2 was treated with plasmapheresis successfully. Triglyceride levels were reduced to less than 500 mg/dL until delivery of healthy babies in both cases.

Conclusion: Omega-3 fatty acids and plasmapheresis may be effective and safe to treat pregnant women with severe hypertriglyceridemia and pancreatitis.

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Introduction

During normal pregnancy, serum total cholesterol can increase by 23% to 53% and triglyceride (TG) by 2- to 4-fold, but for most healthy women with normal baseline serum TG levels such increases are well tolerated. However, in rare instances, certain genetic mutations (ie, apolipoprotein E3/3 genotype, lipoprotein lipase, apolipoprotein E, apolipoprotein C-II genes) can lead to defective coding for proteins and loss of function, leading to different types of dyslipidemia (Table 1). For example, ApoC2 gene mutation(s) lead to apolipoprotein C-II deficiency, which in turn leads to decreased activation of lipoprotein lipase. The clinical consequence of this is a marked decrease in clearance of chylomicrons and TGs from the circulation. Pregnant women can develop hypertriglyceridemia, defined as plasma TG levels above the 95th percentile for age. Mutations of such genes lead to defective coding for proteins and loss of function, leading to clinical conditions that affect health. These patients show an increased risk of developing acute pancreatitis and are also at risk of hypertriglyceridemia in future pregnancies. Pancreatitis caused by hypertriglyceridemia during pregnancy carries a high mortality rate both for the mother (21%) and the fetus (20%). In addition to acute pancreatitis, these patients may also develop hyperviscosity syndrome and possibly preeclampsia. We report 2 pregnant patients with severe hypertriglyceridemia complicated by acute pancreatitis successfully managed with omega-3 acid ethyl esters (Lovaza) and plasmapheresis.

Case Presentation

Case 1

A 33-year-old Caucasian female with a history of recurrent pancreatitis secondary to severe hypertriglyceridemia presented...
for management of dyslipidemia and prediabetes while undergoing in vitro fertilization. She had history of gestational diabetes during her first pregnancy treated with insulin and delivered healthy twins. Family history was significant for premature coronary artery disease in her father at age 30 years and mother at age 52 years. Skin examination did not show any tendon xanthoma, eruptive xanthoma, or xanthelasma. Prior to the visit, her prediabetes and hypertriglyceridemia were previously controlled with metformin, simvastatin, nicotinic acid, and Gemfibrozil used intermittently. She had history of previous hospitalization for acute pancreatitis and serum TG levels of 14 000 mg/dL due to stopping of the hypolipidemic medications. Prior to in vitro fertilization and during her pregnancy, her niacin, simvastatin, Gemfibrozil, and metformin were discontinued by the reproductive endocrinologist because of safety concerns. Patient was counseled on 20% restricted fat diet and prescribed omega-3 acid ethyl ester monotherapy initially on a low dose and after 3 weeks titrating up to 12 g daily (in 3 divided doses). With the strict low-fat diet and high-dose omega-3 acid ethyl esters, her lipid profile was significantly improved, and the serum TG levels remained near normal (Fig. 1). The patient also tolerated the omega-3 acid ethyl esters very well during the pregnancy without adverse effects. She delivered healthy male twins by cesarean section at 37 weeks. After delivery, she was admitted with acute onset of epigastric pain and nausea for 24 hours. On admission, in addition to an elevated serum lipase (505 U/L) and total cholesterol (1651 mg/dL), her TGs were remarkably high (>4000 mg/dL with a 1:5 dilution). She had no family history of hypertriglyceridemia. Abdominal ultrasound showed a small fluid in the left upper quadrant. She was treated with Gemfibrozil 600 mg twice a day, Lovaza (omega-3 acid ethyl esters) 2 g orally twice a day, subcutaneous heparin and insulin, but serum TG levels did not improve. Patient clinical status was worse on the second day in hospital with tachycardia (heart rate 130 bpm), tachypnea (respiratory rate 30) with SpO2 97% on 2 L nasal canula, hypocalcemia (corrected serum calcium 7.4), and persistent high TG above 4425, and the decision was made to inititate plasmapheresis. After the first session, TG levels significantly decreased to 721 mg/dL. On hospital day 6, the TG level rose to 1245 mg/dL, prompting a second plasmaphereses, which lowered the TG level to 770 mg/dL. However, TG again increased to 1365 mg/dL on the next day, which required a third plasmapheresis. For the remainder of hospitalization, patient TG ranged between 400 and 733 mg/dL.

Despite recommendation of a strict fat diet and continuation of Gemfibrozil and Lovaza, her TG continued to be elevated to 1347 mg/dL 5 days later. From that point, she started weekly sessions of preventative plasmapheresis for a total of 8 sessions prior to an uneventful vaginal delivery at 36 weeks of gestation (Fig. 2). One month later, her lipid profile dramatically improved. Total cholesterol was 233 mg/dL and TGs were 304 mg/dL while on the same lipid-lowering regimen.

**Discussion**

During pregnancy, hormonal changes including progesterone, estrogen, and human placental lactogen cause an overall increase in plasma lipids (Table 2). In women with abnormal lipoprotein metabolism these changes lead to severe hypertriglyceridemia and may precipitate pancreatitis. Acute pancreatitis in pregnancy poses various risks to the mother and her fetus. As a result, appropriate treatments to reduce TG levels can minimize maternal and fetal morbidity.

Although a low-fat diet and nutritional support with omega-3 fatty acids and medium-chain TGs remain a cornerstone of therapy, it is necessary to carefully balance fetal nutritional needs and the needs of the mother. An extreme low-fat diet may cause complications of fetal development, such as impaired fetal brain and visual development. Meanwhile, there are limitations on chronic use of lipid-lowering agents such as fibrates and niacin but also other medications, such as insulin and heparin, in pregnancy because of insufficient studies conducted on humans and their risk of teratogenicity. Furthermore, some drugs, such as fibrates, do not provide powerful effects to rapidly decrease the high plasma TG levels. Omega-3 fatty acids and plasmapheresis can be effective and relatively harmless methods that can be used in pregnant women with severe hypertriglyceridemia and pancreatitis (Table 3).

Our first case demonstrates that severe hypertriglyceridemia during pregnancy can be managed with high-dose omega-3 acid ethyl esters and dietary fat restriction. Omega-3 acid ethyl esters down-regulate hepatic lipogenesis and stimulate fatty acid oxidation in the liver and skeletal muscle; hence reducing the TG level. Additionally, omega-3 acid ethyl esters are not incorporated into chylomicrons, directly activate lipoprotein lipase, and enhance removal of TG-rich lipoproteins. Clinically, omega-3 fatty acids have been reported to reduce serum TG by 25% to 30%.

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**Table 1**

| Disorder | Pathogenesis | Lipid phenotype |
|----------|--------------|-----------------|
| Apolipoprotein E mutations | Impaired hepatic uptake of apoE-containing lipoproteins results in reduced conversion of VLDL and intermediate density lipoproteins to LDL, with subsequent accumulation of remnant lipoproteins | Elevations in plasma total cholesterol and TGs |
| Apolipoprotein A-V deficiency (APOA5 mutation) | Impaired VLDL apoB-100 catabolism | Hypertriglyceridemia |
| Apolipoprotein C-II deficiency (APOC2 mutation) | Decreased activation of lipoprotein lipase | Marked hypertriglyceridemia/ chylomicronemia in infancy or childhood |
| LPL deficiency | Loss of functional LPL results in reduced hydrolysis of chylomicron- and VLDL-TGs | Very high TG levels and features of the chylomicronemia syndrome |
| LMF1 mutation | Loss of functional LMF1, which traverses the endoplasmic reticulum and assists with the correct folding and maturation of LPL | Chylomicronemia later in adulthood |
| GPIHBP1 mutation | Loss of functional GPIHBP1 that stabilizes binding of chylomicron near LDL and supports lipolysis Chylomicronemia later in adulthood | |

**Abbreviations:** GPIHBP1 — glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; HDL — high density lipoprotein; LDL — low density lipoprotein; LMF1 — lipase maturation factor 1; LPL — lipoprotein lipase; TG — triglyceride; VLDL — very low density lipoprotein.

*Derived from reference 3.

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**Case 2**

A 28-year-old primigravida patient at 29th week gestation was admitted with acute onset of epigastric pain and nausea for 24 hours. On admission, in addition to an elevated serum lipase (505 U/L) and total cholesterol (1651 mg/dL), her TGs were remarkably high (>4000 mg/dL with a 1:5 dilution). She had no family history of hypertriglyceridemia. Abdominal ultrasound showed a small amount of fluid in the left upper quadrant. She was treated with Gemfibrozil 600 mg twice a day, Lovaza (omega-3 acid ethyl esters) 2 g orally twice a day, subcutaneous heparin and insulin, but serum TG levels did not improve. Patient clinical status was worse on the second day in hospital with tachycardia (heart rate 130 bpm), tachypnea (respiratory rate 30) with SpO2 97% on 2 L nasal canula, hypocalcemia (corrected serum calcium 7.4), and persistent high TG above 4425, and the decision was made to initiate plasmapheresis. After the first session, TG levels significantly decreased to 721 mg/dL. On hospital day 6, the TG level rose to 1245 mg/dL, prompting a second plasmaphereses, which lowered the TG level to 770 mg/dL. However, TG again increased to 1365 mg/dL on the next day, which required a third plasmapheresis. For the remainder of hospitalization, patient TG ranged between 400 and 733 mg/dL.

Despite recommendation of a strict fat diet and continuation of Gemfibrozil and Lovaza, her TG continued to be elevated to 1347 mg/dL 5 days later. From that point, she started weekly sessions of preventative plasmapheresis for a total of 8 sessions prior to an uneventful vaginal delivery at 36 weeks of gestation (Fig. 2). One month later, her lipid profile dramatically improved. Total cholesterol was 233 mg/dL and TGs were 304 mg/dL while on the same lipid-lowering regimen.
Based on a small number of case reports, omega-3 acid ethyl esters are generally safe.\textsuperscript{11,12} Omega-3 acid ethyl esters are given in 3 to 4 g daily together with dietary fat restriction to treat severe hypertriglyceridemia during pregnancy.\textsuperscript{7} However, there are some data on higher doses that have been used. For example, Glueck et al\textsuperscript{11} effectively treated a pregnant patient with 12 g eicosapentaenoic acid without adverse effects. As shown in Fig 1, our patient’s serum TG was well controlled throughout the pregnancy with 12 g of Lovaza in divided doses along with a meal plan limiting fat to 20% of ingested calories. Although we exceeded the recommended dose of Lovaza by 3-fold, there were adverse effects after a short time either in the mother or the baby.

Our second case illustrates severe hypertriglyceridemia complicated by acute pancreatitis that was successfully treated with plasmapheresis. Plasmapheresis works by decreasing TG levels (up to 70\% in 1 session), reducing inflammatory cytokines, and replacing deficient lipoprotein lipase or apolipoproteins when plasma is used as the replacement fluid.\textsuperscript{13} Plasmapheresis also removes excessive proteases from the plasma and replaces consumed protease-inhibitors. Due to lack of evidence, plasmapheresis can be considered within category III by the American Society of Apheresis and in cases where hypertriglyceridemia is severe and refractory to all other therapies.\textsuperscript{14,15} In our second patient, other treatment regimens including Gemfibrozil, Lovaza, and parenteral insulin were used.
without efficacy. At this point, plasmapheresis was started and provided a significant decrease by over 80% TG level after the first session.

Due to limited data available on using plasma exchange during pregnancy, current knowledge about its effectiveness and safety is based on expert opinions and case reports (Table 4). While most of the cases required cesarean section, our case had uneventful vaginal delivery. Plasmapheresis can be utilized not only in severe gestational hypertriglyceridemia complicated by pancreatitis but also prophylactically in patients with recurrent pancreatitis.2 Most patients needed multiple sessions of plasmapheresis because its effect is usually transient.2 Our case had a repeated rise in TG levels, which required multiple sessions of plasmapheresis. Plasmapheresis is generally well tolerated in pregnant patients. Some concerns arise from the central venous access for procedures and its subsequent infection risk, transient anticoagulation due to loss of clotting factors that poses risk of obstetric hemorrhage, and placental perfusion due to fluid volume shift.17 Additionally, the incidence of adverse effects including blood access problems, tingling, hypotension, and urticaria is reported to be 5.7%.18 Another potential concern of plasmapheresis is the safety limit of fluid volume shift.17

Table 2
Hormone Changes in Pregnancy and Their Impact on the Lipid Panelb

| Hormone change during pregnancy | Effects on lipid panel | Mechanism |
|--------------------------------|------------------------|-----------|
| Estrogen (increase)            | Increase TG and VLDL   | • Decrease in the LPL gene expression inhibits LPL activity and reduces the VLDL cholesterol clearance. |
| Progesterone (increase)        | Increase TG-rich lipoprotein secretion and VLDL cholesterol | • Increase in hepatic lipase activity enhances TG and VLDL synthesis in the liver |
| Prolactin (increase)           | Increase TG            | • Increase lipogenesis |
| Human placental lactogen (increase) | Increase free fatty acids | • Suppress hepatic lipase activity |
| Insulin (increase progressively from 1st to 3rd trimester) | Accumulate maternal fat depots | • Insulin insensitivity increases during the 1st trimester, but decreases during the second and third trimesters. |
| Leptin (increase)              | Increase TG, total cholesterol, and LDL levels | • Insulin sensitivity increases during the 1st trimester, but decreases during the second and third trimesters. |
| Adiponectin (decrease)         | Increase TG, total cholesterol, and LDL levels | • Insulin sensitivity increases during the 1st trimester, but decreases during the second and third trimesters. |
| Cortisol (increase)            | Increase TG, total cholesterol, and LDL levels | • Insulin sensitivity increases during the 1st trimester, but decreases during the second and third trimesters. |

Table 3
Considerations for Management of Hypertriglyceridemia During Pregnancya

| Treatment modalities | Mechanism and effects | Limitations |
|----------------------|-----------------------|-------------|
| Low-fat diet         | <20% of calories from fat helps reduce chylomicrons (substrates for exogenous TG synthesis pathway) | A small risk of low birth weight, prematurity and maternal complications from extreme weight loss |
| Omega-3 acids        | Decrease hepatic TG synthesis, increase peroxisomal β-oxidation, enhance LPL activity and adipose tissue LPL expression | Fishy taste |
| Fibrates             | Increase LPL level, decrease hepatic TG synthesis by induction of hepatic free fatty acid oxidation, and stimulation of reverse cholesterol transport | Mild gastrointestinal side effects (eg, eructation) |
| Niacin-based preparations | Decrease hepatic TG synthesis | Slow onset |
| Heparin              | Release LPL from the endothelium into the plasma | May cause teratogenicity during first semester |
| Insulin              | Rapid and potent activator of LPL | High dose to treat hypertriglyceridemia has not been studied in pregnant patients |
| Therapeutic plasma exchange | Rapidly remove TG-rich lipoprotein | Transient effect |

Abbreviations: HDL – high density lipoprotein; LDL – low density lipoprotein; LPL – lipoprotein lipase; TG – triglyceride; VLDL – very low density lipoprotein.

a Derived from reference 5.

b The changes of lipid profiles during pregnancy are affected by the dominant actions of estrogen, progesterone, placental lactogen, and prolactin. In patients with genetic mutations, these effects on lipid profiles will be much more significant.
Cases of Gestational Hypertriglyceridemia-Induced Pancreatitis Managed With Therapeutic Plasma Exchange

| Case                  | Patient age (years) | Time of pancreatitis during gestation | Treatment regimen                  | Total sessions required | Clinical outcome                                  |
|----------------------|---------------------|---------------------------------------|------------------------------------|-------------------------|--------------------------------------------------|
| Our patient (case 2) | 28                  | 29 weeks                              | Therapeutic plasma exchange        | 8                       | An uneventful vaginal delivery at 36 weeks of gestation |
| Michalova et al20    | 27                  | 22 weeks, 27 weeks, and 33 weeks of 1st pregnancy; 17 weeks of 2nd pregnancy | Therapeutic plasma exchange        | 17                      | Delivered a healthy baby at 36 weeks of gestation by C-section |
| Serpytis et al21     | 31                  | 33 weeks                              | Therapeutic plasma exchange        | 3                       | Delivered a healthy newborn female by C-section   |
| Huang et al22        | Mean age 27.6       | Unknown                               | Therapeutic plasma exchange (fresh frozen plasma or albumin) | 1-3                     | Delivery of 4 healthy infants via C-section Termination of pregnancy at 21 weeks in 1 case |

Conclusion

Severe gestational hypertriglyceridemia is a common cause of pancreatitis that can cause complications during pregnancy. Management of gestational hypertriglyceridemia requires multidisciplinary care with mainstays of a low-fat diet and antilipidemic regimens. Omega-3 fatty acids are safe for pregnancy use as monotherapy, even at a high dose. Plasmapheresis can be safe and efficacious when nutrition therapy and other standard medical interventions fail; however, additional research is needed.

Disclosure

The authors have no multiplicity of interest to disclose.

Acknowledgment

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