Endocrinology, Diabetes & Metabolism CASE REPORTS

A S Kim and others | TPE for gestational hypertriglyceridaemia

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Therapeutic plasma exchange for the management of severe gestational hypertriglyceridaemic pancreatitis due to lipoprotein lipase mutation

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Summary

A 19-year-old female presented at 25-weeks gestation with pancreatitis. She was found to have significant hypertriglyceridaemia in context of an unconfirmed history of familial hypertriglyceridaemia. This was initially managed with fasting and insulin infusion and she was commenced on conventional interventions to lower triglycerides, including a fat-restricted diet, heparin, marine oil and gemfibrozil. Despite these measures, the triglyceride levels continued to increase as she progressed through the pregnancy, and it was postulated that she had an underlying lipoprotein lipase defect. Therefore, a multidisciplinary decision was made to commence therapeutic plasma exchange to prevent further episodes of pancreatitis. She underwent a total of 13 sessions of plasma exchange, and labour was induced at 37-weeks gestation in which a healthy female infant was delivered. There was a rapid and significant reduction in triglycerides in the 48 h post-delivery. Subsequent genetic testing of hypertriglyceridaemia genes revealed a missense mutation of the *LPL* gene. Fenofibrate and rosuvastatin was commenced to manage her hypertriglyceridaemia postpartum and the importance of preconception counselling for future pregnancies was discussed. Hormonal changes in pregnancy lead to an overall increase in plasma lipids to ensure adequate nutrient delivery to the fetus. These physiological changes become problematic, where a genetic abnormality in lipid metabolism exists and severe complications such as pancreatitis can arise. Available therapies for gestational hypertriglyceridaemia rely on augmentation of LPL activity. Where there is an underlying LPL defect, these therapies are ineffective and removal of triglyceride-rich lipoproteins via plasma exchange should be considered.

Learning points:

- Hormonal changes in pregnancy, mediated by progesterone,oestrogen and human placental lactogen, lead to a two- to three-fold increase in serum triglyceride levels.
- Pharmacological intervention for management of gestational hypertriglyceridaemia rely on the augmentation of lipoprotein lipase (LPL) activity to enhance catabolism of triglyceride-rich lipoproteins.
- Genetic mutations affecting the *LPL* gene can lead to severe hypertriglyceridaemia.

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- Therapeutic plasma exchange (TPE) is an effective intervention for the management of severe gestational hypertriglyceridaemia and should be considered in cases where there is an underlying LPL defect.
- Preconception counselling and discussion regarding contraception is of paramount importance in women with familial hypertriglyceridaemia.

Background

Hormonal changes in pregnancy lead to a two- to three-fold increase in serum triglyceride levels (1, 2). In women with normal baseline triglyceride levels and normal lipid metabolism, this increase is not clinically significant and no specific intervention is required. However, women with rare genetic abnormalities that affect triglyceride metabolism may develop gestational hypertriglyceridaemia which can be severe and associated with acute complications including pancreatitis, pre-eclampsia or fetal demise (3, 4).

Lipoprotein lipase (LPL) mediates catabolism of triglyceride-rich lipoprotein: very-low-density lipoprotein (VLDL) and chylomicrons. Familial chylomicronaemia syndrome is usually caused by mutations in the lipoprotein lipase (*LPL*) gene, that is, LPL deficiency, with rarer causes being due to mutations in genes responsible for maturation, transport and surface expression of *LPL* (5, 6).

Here, we present a female whose pregnancy has been complicated by severe hypertriglyceridaemic pancreatitis in the context of a homozygous *LPL* mutation.

Case presentation

A primiparous 19-year-old Lebanese female presented at 25-weeks gestation with worsening abdominal pain and nausea. She was known to have hypertriglyceridaemia diagnosed in infancy following an episode of pancreatitis at the age of 3 years and was previous prescribed medium chain triglyceride (MCT) supplementation during adolescence.

Her family history was significant for hypertriglyceridaemia, affecting her younger brother and a paternal cousin who developed pancreatitis in childhood. Our patient was a child of consanguineous parents. There was no family history of diabetes or early-onset coronary artery disease or cerebrovascular accidents. She did not display eruptive xanthoma, lipaemia retinalis or hepatosplenomegaly.

Investigation

Prior to this pregnancy, her baseline triglycerides fluctuated between 10.0 and 25.0 mmol/L (886.0 to 2214.0 mg/dL). Her preconception weight was 60 kg with a BMI of 22 kg/m^2 ,and triglycerides shortly following conception was 25.6 mmol/L (2268.0 mg/dL).

At 25-weeks gestation, the patient developed fevers and abdominal pain. Bloods revealed leucocytosis 15.4 × 10^9/L (RR: 3.9–11.1 × 10^9/L), c-reactive protein 200 mg/L (RR: <3 mg/L) as well as raised lipase 687 U/L (RR: <400 U/L). Her lipid profile showed triglycerides 41.4 mmol/L (3667.0 mg/dL; RR: <2.0 mmol/L) and elevated cholesterol of 9.3 mmol/L (360.0 mg/dL; RR: 3.0–5.5 mmol/L) (Fig. 1). Ultrasonography revealed a bulky pancreas with peripancreatic free fluid, and the liver had normal sonographic appearance. There was no cholelithiasis or evidence of pyelonephritis.

Treatment

A diagnosis of hypertriglyceridaemic pancreatitis was made and insulin infusion was commenced, in addition to s.c. heparin (5000 IU three times daily) and marine oil (9 g daily), and the subject was kept in a fasting state for 72 h, following which she was commenced on a fat-restricted diet (<10 g/day). Betamethasone was administered to promote fetal lung maturation. The triglycerides improved and reached a nadir of 10.0 mmol/L (886.0 mg/dL). Insulin was ceased and gemfibrozil was commenced at 200 mg TDS.

Despite these measures, the triglyceride levels increased to 24.0 mmol/L (2126.0 mg/dL) in the course of a week. This was concerning for a potential LPL defect due to rise in the triglycerides despite pharmacotherapy to enhance LPL activity. Due to risk of recurrent pancreatitis with persistently elevated triglycerides and increasing concerns with weight loss on such an intensive fat-restricted diet, a multidisciplinary decision was made to pursue therapeutic plasma exchange (TPE).

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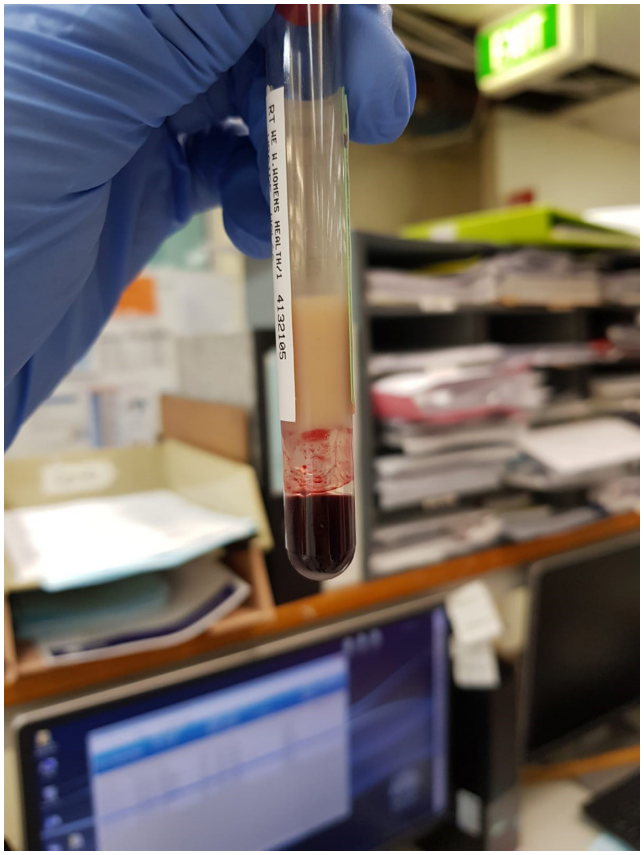

Figure 1
Patient's blood following centrifugation. Note the layer of lipaemic plasma.

Central venous access was established and the first TPE was performed at 28-weeks gestation, in which 2500 mL of plasma was exchanged with 4% albumin, achieving a reduction in triglycerides from 25.0 mmol/L (2214.0 mg/dL) to 13.0 mmol/L (1152.0 mg/dL) (Fig. 2). She continued to undertake weekly TPE, which she tolerated well. However, following four sessions of TPE, and as she entered her third trimester, the peaks and trough

Figure 2
Approximately 2500 mL of lipaemic plasma following a session of therapeutic plasma exchange (TPE).

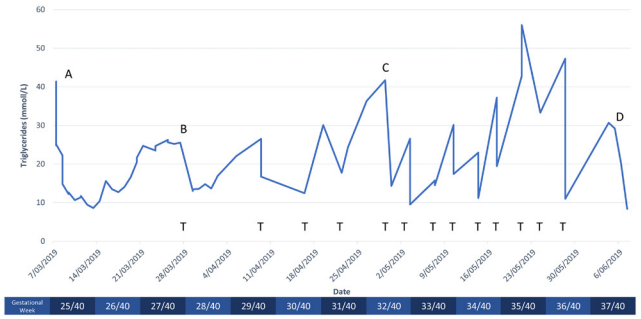

Figure 3
Serum triglycerides throughout pregnancy. Pancreatitis (A) followed by commencing therapeutic plasma exchange (B) and increased frequency of TPE to twice weekly (C) until delivery (D). TPE sessions marked by T.

triglycerides began to rise (Fig. 3). The frequency of TPE was escalated to twice weekly at 32-weeks gestation and the triglycerides peaked at 56.0 mmol/L (4960.0 mg/dL) at 35-weeks gestation, although pancreatitis was avoided at this time. She required a total of 13 TPE sessions throughout her pregnancy.

During this period, fetal ultrasound and cardiotocography (CTG) were reassuring in excluding fetal distress or growth problems. The estimated fetal weight remained between 30–56th centile on ultrasonography between 25- and 36-weeks' gestation. The amniotic fluid index (AFI) and umbilical artery resistance was appropriate for gestation age at each scan.

Outcome and follow-up

Labour was induced at 37-weeks gestation, resulting in the delivery of a female infant weighing 2940 g with Apgar scores of 9 at 1 and 5 min following birth. A rapid and significant reduction in triglycerides from 30.0 mmol/L (2657.0 mg/dL) to 8.0 mmol/L (709.0 mg/dL) was noted over 48 h postpartum and she did not require any further TPE (Fig. 3).

Massive parallel sequencing with targeted analysis of hypertriglyceridaemia genes (*LPL*, *APOA5*, *APOC2*, *APOE*, *LMF1*, *GPIHBP1*, *PPARG*, *LMNA*, *APOC3*, and *GPD1*) was performed following delivery. Our patient was found to be homozygous for a missense mutation in exon 5 of *LPL* (NM_000237.2: c.602A>T, p.Asp201Val), classified as 'likely pathogenic'.

The patient was commenced on fenofibrate 145 mg daily and continues on a fat-restricted diet and marine oil supplementation. Rosuvastatin was then added due to ongoing hypertriglyceridaemia to 9.0 mmol/L (797.0 mg/dL). The importance of preconception

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counselling for future pregnancies was discussed and an intrauterine device (IUD) contraception was implanted.

Discussion

Hormonal changes in pregnancy, particularly those mediated by progesterone, estrogen and human placental lactogen, lead to an overall increase in plasma lipids (7). The physiological basis of these hormone-induced lipid changes is to ensure adequate energy source in the mother to ensure nutrient delivery to the fetus. These physiological changes in serum triglyceride levels can be problematic when a genetic abnormality in lipid metabolism exists (familial hypertriglyceridaemia), leading to gestational hypertriglyceridaemia (GHT). Complications arising from gestational hypertriglyceridaemia include pancreatitis preterm labour, pre-eclampsia and fetal death *in utero*.

Two main mechanisms have been proposed to explain the pathophysiology of hypertriglyceridaemic pancreatitis. First is the development of pancreatitis by acidosis and ischaemia secondary to free fatty acid (FFA) toxicity. Excess triglyceride-rich chylomicrons are hydrolysed within the pancreas which release high levels of free fatty acids. The unbound FFAs can cause damage to the vascular endothelium and acinar cells resulting in pancreatitis (8, 9). Secondly, excess chylomicronaemia leads to increase in plasma viscosity which can lead to capillary plugging and ischaemia which can also eventually trigger pancreatitis (8, 9).

Details of 17 reported cases of gestational hypertriglyceridaemic pancreatitis (GHTP) managed with plasma exchange are summarised in Table 1, which demonstrate the onset of pancreatitis typically in the second and third trimester (10, 11, 12, 13, 14, 15, 16, 17,

Table 1 Cases of gestational hypertriglyceridaemic pancreatitis managed with therapeutic plasma exchange.

Case	Patient age (years)	Time of pancreatitis during gestation	Treatment regimen	Total sessions required	Clinical outcome
Our case	19	25 weeks	TPE (albumin)	13	Successful vaginal delivery of health infant at 37 weeks
Swoboda *et al*. (10)	23	24 weeks	Combined TPE (albumin) and LDL apheresis	10	2nd episode of pancreatitis at 32 weeks. Emergency caesarean section (CS) at 36 weeks due to impairment of umbilical blood flow.
Bildirici *et al.* (11)	26	24 weeks	TPE (replacement not reported)	3	Emergency CS due to fetal distress with subsequent infant death. Maternal pseudocyst formation.
Achard *et al*. (12)	30	26 weeks	Combined TPE (albumin) and LDL apheresis	2	Vaginal delivery of healthy infant at 34 weeks
Saravanan *et al.* (13)	30	34 weeks	TPE (albumin)	2	Emergency CS due to fetal distress and pre-eclampsia. Delivery of health infant. Maternal course complicated by septic shock.
Yamauchi *et al.* (14)	23	27 weeks	TPE (replacement not reported)	2	Emergency CS due to fetal distress. Delivery of healthy infant.
Exbrayat *et al.* (15)	31	33 weeks	TPE (replacement not reported)	1	Emergency CS due to fetal distress. Delivery of healthy infant.
Altun *et al.* (16)	27	5 weeks	TPE (FFP)	3	Fetal demise at 6 weeks.
	24	27 weeks	TPE (FFP)	14	CS at 34 weeks with delivery of healthy infant.
Safi *et al.* (17)	24	28 weeks	TPE (albumin)	9	CS at 35 weeks due to lack of reduction of TG with TPE. Delivery of healthy infant.
Lim *et al.* (18)	27	23 weeks	TPE (albumin)	4	Preterm birth with placental abruption at 33 weeks.
Huang *et al.* (19)	Mean age 27.6	Unknown	TPE (FFP or albumin)	1-3	Delivery of 4 healthy infants via CS. Termination of pregnancy at 21 weeks in one case.
Chyzhyk *et al.* (20)	28	20 weeks	TPE (replacement not reported)	Not reported	Vaginal delivery of healthy infant at 36 weeks.

CS, Caesarean Section; FFP, Fresh Frozen Plasma; LDL, Low-Density Lipoprotein; TPE, Therapeutic Plasma Exchange.

18, 19, 20). The majority of cases (11/17, 65%) required emergency caesarean section due to fetal distress or complications. Our case is significant as successful early-term vaginal delivery was achieved after multiple TPE sessions throughout pregnancy.

The treatment strategy in our case involved the use of TPE to prevent recurrent pancreatitis for the remainder of the pregnancy. In comparison to published reports on the occurrence of hypertriglyceridaemic pancreatitis in pregnancy, unique features of our case include the use of TPE to reduce the risk of hypertriglyceridaemic pancreatitis, targeting a more liberal triglyceride target of preconception levels, delivery at near term through normal vaginal delivery and the identification of an LPL mutation implicated in familial hypertriglyceridaemia. It is important to note that, while TPE is generally well tolerated in pregnancy, there are concerns for the need for central venous access and its associated infection risk, transient anticoagulation related to loss of clotting factors, risk of obstetrics haemorrhage and the potential changes to placental perfusion due to changes in fluid volume. We performed continuous fetal monitoring during TPE sessions and were well tolerated by the mother and the fetus.

Genetic studies have identified that patients with severe hypertriglyceridaemia typically present in childhood and adolescence and display classic autosomal recessive pattern of inheritance. These patients are homozygous or compound heterozygous for large-effect, loss-of-function mutations in genes that regulate catabolism of triglyceride-rich lipoproteins. These include genes coding LPL – which mediate catabolism of chylomicrons and very-low-density-lipoproteins (VLDL), apolipoproteins C-II and A-V (*APOC2*, *APOA5*) – which activate LPL and genes responsible for maturation, transport and surface expression of LPL (*LMF1*, *GPIHBP1*) (5).

In our case, a homozygous LPL variant p.Asp201Val was identified. Asp201 occurs in a highly conserved region encoded by exon 5, and Asp201Val is predicted to be pathogenic by *in silico* algorithms (PolyPhen2, SIFT, MutationTaster). Other pathogenic missense variants in LPL exon 5 have been demonstrated to affect protein folding and stability (21) or interfere with access of the lipid substrate into the catalytic pocket of this important enzyme. (22) A recent crystallography study showed that the carboxylic acid side chain of D201 participates in the coordination of LPL's calcium ion via an ordered water molecule. A valine in the same position cannot participate in calcium coordination, providing data on the mechanism of disease in the case of the Asp201Val mutation (23). Interestingly, Asp201Val has been described in two Lebanese patients (aged 7 and 34 years) with LPL deficiency and a history of acute pancreatitis (24).

This is particularly significant as our patient and her husband are second cousins, which confers risk of inheritance of homozygous pathogenic *LPL* mutations in the new-born. Genetic testing for the infant and the husband is underway.

The available therapies for gestational hypertriglyceridaemia, such as omega-3 fatty acids, gemfibrozil and insulin, predominantly rely on the augmentation of lipoprotein lipase activity to catabolise triglyceride-rich lipoproteins (25). It is important to note that the fetal risk of the use of gemfibrozil during pregnancy is unclear and the lack of response to gemfibrozil and other therapeutic options led us to postulate a LPL mutation. Treatment of LPL deficiency is based on medical nutrition therapy with restriction of dietary fat to less than 20 g per day to reduce plasma triglyceride concentration (5). However, given the episode of pancreatitis and persistent hypertriglyceridaemia, despite strict fat restriction in the context of pregnancy, treatment was escalated to TPE.

Novel therapies for the management of familial lipoprotein lipase deficiency include alipogene tiparvovec, a gene therapy in which a viral vector is utilised to deliver intact LPL genes into muscle cells (26). While there was significant reduction in serum triglyceride levels following its use, it was prohibitively expensive and is no longer available.

Sequencing studies of exomes – which are protein coding regions of the human genome – have identified the association between apolipoprotein C3 (APOC3) mutation and lower triglyceride levels. Carriers of this mutation were found to have a reduced risk of coronary heart disease (27). Volanesorsen is an antisense inhibitor of APOC3 synthesis which lowers plasma APOC3 and triglyceride levels. Use of volanesorsen has been associated with significant reduction in triglyceride levels in patients with familial hyperchylomicronaemia (28), though the efficacy and safety for its use during pregnancy remains to be seen.

Our case highlights the use of TPE as an effective treatment for GHT, which should be considered in cases where usual augmentation of LPL cannot be utilised due to an LPL mutation, and highlights successes in delivering a healthy fetus near term, with a more liberal triglyceride target without acute maternal or fetal complications.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent has been obtained from the patient for publication of the submitted article.

Author contribution statement
A S K wrote the manuscript. A S K, R H, A A, M C T, T I A and C M G treated the patient and contributed to the manuscript. A J H conducted and interpreted genetic testing and contributed to the manuscript. All authors reviewed the manuscript.

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