Therapeutic plasma exchange in secondary prevention of acute pancreatitis in pregnant patient with familial hyperchylomicronemia

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Introduction. Hormone changes during pregnancy lead to increased plasma lipid levels. When there is added disorder of lipid metabolism, this otherwise physiological change can cause extremely high triglyceride levels with potentially life-threatening complications, such as non-biliary acute pancreatitis.

Materials and Methods. We present a case report of a 27-year-old pregnant woman with familial hyperchylomicronemia and a history of 7 hypertriglyceridemia-induced acute pancreatitis attacks. Three attacks occurred during her first pregnancy with the last one leading to its termination at 33 weeks owing to the death of the fetus. During her second pregnancy, standard treatment was not able to lower the triglyceride levels sufficiently and she suffered another acute pancreatitis attack. Therapeutic plasma exchange was therefore chosen as the treatment method.

Results and Conclusion. Plasma exchange was successful in the secondary prevention of acute pancreatitis attack and she delivered a healthy baby at 36 weeks of gestation. Treatment was very well tolerated by the mother and the fetus and this supports the use of apheresis as a safe and efficient method in tackling gestational hypertriglyceridemia.

Key words: acute pancreatitis, hypertriglyceridemia, pregnancy, therapeutic plasma exchange

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INTRODUCTION

Due to hormonal changes during pregnancy all plasma lipids increase following the first eight weeks to ensure adequate nutrition of the fetus. Triglyceride (TG) levels are the most affected, rising 2-3 fold by the third trimester, with mean triglyceride levels of 0.89 mmol/L in first, 1.71 mmol/L in second and 2.77 mmol/L in the third trimester 1-3. Although these changes are physiological and usually pose no medical problem, when there are preexisting disorders of lipid metabolism, TGs may reach extremely high levels and become a threat for mother and fetus 4. Severe gestational hypertriglyceridemia is arbitrarily defined as a TG level above 11.3 mmol/L, as higher levels of TG are associated with increased risk of acute non-biliary pancreatitis 5.

It is estimated that acute pancreatitis occurs in 1 in 1,000 to 1 in 12,000 pregnancies 6. Severe hypertriglyceridemia is considered one of its main causes 7,8 and some sources report it as the underlying etiology in 27.5-50% of all cases 8. Although it is rare, it poses a significant risk. While contemporary mortality rates are lower than in the past, complications such as pancreatic necrosis, acute respiratory distress syndrome, preeclampsia, shock, fetal death in utero, preterm labor and others should not be underestimated 9,10.

The pathophysiological mechanism of acute pancreatitis induced by hypertriglyceridemia is not completely understood. It has been proposed that fatty acids produced by hydrolysis of TG by pancreatic lipase have a toxic effect on the acinar cells of the pancreas and the capillaries. Additionally, chylomicrones cause congestion in the capillaries of the pancreas leading to ischemia and acidosis. The overall state results in activation of tripsynogen and therefore in acute pancreatitis 11.

CASE REPORT

A 27-year-old woman at the 24 weeks of her second pregnancy was admitted to our department because of severe refractory hypertriglyceridemia. She was diagnosed with familial hyperchylomicronemia due to lipoprotein lipase deficiency as a child. Genetic testing confirmed a recessive missense mutation from her mother (c.644G>A) and a novel mutation from her father c.841_842delAA, which led to creation of a premature stop codon at the 281st position, leading to premature termination of lipoprotein lipase synthesis and creation of the shortened non-functional form. Interestingly, the patient and unborn child’s father were second cousins but he was not a lipoprotein lipase mutation carrier.
Her medical history also revealed recurrent acute pancreatitis, overall 7 times, with subsequent progression to chronic pancreatitis with pseudocysts. 3 of the attacks occurred during the course of her first pregnancy 4 years ago. The first two attacks occurred at 22 and 27 weeks with TG levels on admission of 10.4 mmol/L and 44.16 mmol/L respectively. Supportive treatment such as withholding oral feeding, intravenous fluid infusion and spasmoanalgesic therapy was sufficient and attacks subsided gradually. The third attack at 33 weeks with a TG level of 84 mmol/L was associated with thrombosis of the portal vein and resulted in pregnancy termination by Caesarean section due to the death of the fetus. After the termination, the TG level decreased significantly to 4.4 mmol/L. Another pregnancy was considered high-risk and was not advised.

During the course of the second pregnancy, her TG levels had again risen (Fig. 1) and despite the established nutritional regimen, she already suffered a mild pancreatitis attack at 17 weeks with a TG level of 27.3 mmol/L. Once again, supportive treatment was sufficient and the attack subsided gradually.

On admission, she was feeling well. Neither abdominal pain nor dyspepsia were reported. On physical examination, no special sign was found. Her body mass index (BMI) was 20.96 kg/m² before pregnancy. Laboratory
findings showed lipase level and inflammatory markers within normal limits, amylase level was 1.74 ukat/L, TG 18.56 mmol/L; cholesterol 5.95 mmol/L; high-density lipoprotein (HDL) cholesterol 0.78 mmol/L, low-density lipoprotein (LDL) cholesterol could not be assessed. Mild normocytic anemia was also found.

Medical nutrition therapy continued with dietary fat/day reduction to less than 30 g/day in association with omega-3 fatty acids including eicosapentanoic acid and docosahexaenoic acid in dose of 225 mg/day and 170 mg/day respectively. Intermittent supervised fasting associated with intermittent total parenteral nutrition was started with dual chambre bags containing amino acids and glucose with electrolytes. Fat-soluble vitamins were supplemented and to prevent iron deficiency anaemia, iron supplements were also given. Fibrate could not be added to treatment due to the lipoprotein lipase deficiency.

Despite medical therapy TG levels remained high (> 18.56 mmol/L). With the aim of achieving a safe TG level and to prevent another attack of acute pancreatitis after multidisciplinary consultation, therapeutic plasma exchange (TPE) was initiated. Membrane plasma exchange every 3 to 7 days (mean interval 4.25 days) was performed. From 24 to 36 weeks the patient underwent 17 apheresis in total (Fig. 2). During one session 2,000 mL of plasma were removed and then replaced with 1,600 mL of Ringer’s solution and 400 mL of 20% human albumin. When measured immediately after the session, the lowest TG level was 9.91 mmol/L and the mean decrease was 33.27% (Table 1). Overall, the lowest TG level achieved was 5.36 mmol/L. Later on, because of the rising lipid levels at the end of pregnancy, TG levels started to rise even with TPE. Also complications, such as low blood flow, high transmembrane pressure occurred during the later TPE and the last session was associated with insufficient blood flow.

Due to technical complications and high risk of acute pancreatitis recurrence, at 36 weeks elective Caesarean section was performed and a borderline immature but sufficient blood flow, high transmembrane pressure occurred during the later TPE and the last session was associated with insufficient blood flow.

When performed in pregnant women, most reported cases use TPE in cases of acute pancreatitis, while only a small number of cases used it as a prophylactic measure. There are no clear recommendations given by the American Society of Apheresis, so various regimes were used. In cases employing therapeutic plasma exchange as a preventive measure, 3 patients had a positive medical history for acute pancreatitis. There was a wide variability in the timing of the first TPE (from 16 to 33 weeks) and also in the total number of sessions (from 3 to 41) (median 13). The most frequently used modality was therapeutic plasma exchange alone, in one case a combination of therapeutic plasma exchange and double filtration plasmapheresis, and in one case, only double filtration plasmapheresis was performed. All treatments led to the birth of healthy infants. Two pregnancies ended in preterm delivery at 34 and 36 weeks, by induction of labour due to uncontrollable TG levels and elective Caesarean section respectively. Other term infants were born mostly by elective Caesarean section, only one at 38 weeks by spontaneous vaginal delivery.

Severe gestational hypertriglyceridemia is defined as TG levels above 11.3 mmol/L. However this is arbitrarily stated and safe limits for pregnant women are still a subject of discussion. Some women may tolerate higher levels of TG but there are also reported cases of acute pancreatitis occurring with TG levels between 5.65 mmol/L to 11.3

### Table 1. Decrease of triglyceride level, when measured immediately after the therapeutic plasma exchange (TPE).

| Day 9  | First TPE  | 20.92 | 15.23 | 27.19 |
| Day 12 | Second TPE | 20.64 | 12.61 | 38.9  |
| Day 31 | Seventh TPE| 16.22 | 9.91  | 38.9  |
| Day 59 | Thirteenth TPE | 22.92 | 16.48 | 28.09 |

**DISCUSSION**

Treatment of gestational hypertriglyceridemia is problematic. Low-fat diet and nutritional support with omega-3 fatty acids and medium-chain triglycerides is a cornerstone of therapy but careful balancing of fetal nutritional needs and the needs of the mother is required. Use of lipid lowering agents, such as fibrates and niacin but also other medication, such as insulin and heparin, remains controversial.

Therapeutic plasma exchange for treatment of hypertriglyceridemic pancreatitis is considered a category III indication by the American Society of Apheresis due to low quality evidence (2C) (ref.12). One of the largest studies concerning the use of therapeutic plasma exchange for hypertriglyceridemia induced pancreatitis was published in the United States in 2016. It analysed the clinical data from 13 cases of hypertriglyceridemia induced pancreatitis in 12 patients who underwent single therapeutic plasma exchange procedure to reduce plasma triglyceride levels. They report its effectiveness with a TG level reduction of 84% and possibly also a decrease in the length of the hospital stay.

When measured immediately after the session, the lowest TG level was 9.91 mmol/L and the mean decrease was 33.27% (Table 1). Overall, the lowest TG level achieved was 5.36 mmol/L. Later on, because of the rising lipid levels at the end of pregnancy, TG levels started to rise even with TPE. Also complications, such as low blood flow, high transmembrane pressure occurred during the later TPE and the last session was associated with insufficient blood flow.

Due to technical complications and high risk of acute pancreatitis recurrence, at 36 weeks elective Caesarean section was performed and a borderline immature but healthy male baby was delivered, with a birth weight 2560 g and Apgar score 8 in the 1st and 5th minute. In the postnatal period however, he suffered from bronchopneumonia with the need for continuous positive airway pressure (CPAP) and oxygen inhalation for 5 days but it was successfully treated with a combination of intravenous antibiotics (ampiciline and gentamycine).

Maternal serum TG level decreased immediately from 26.7 mmol/L before the delivery to 12.46 mmol/L.
mmol/L (ref. 6,25,26). Therefore the target value in treatment of hypertriglyceridemia to prevent acute pancreatitis is 11.3 mmol/L (ref. 4,14). Some authors advocate value 5.65 mmol/L as a safer option37, though. While some advocate a more aggressive approach with a clear goal-driven protocol23, others due to complications of TPE, such as severe iron deficiency anemia, choose higher goal TG levels4. Similarly variable intervals between TPE sessions are reported.

In our case, TPE twice weekly led to a decrease in TG levels below 11.3 mmol/L and then below 5.65 mmol/L. To maintain the TG level and to decrease risk of TPE associated complications, sessions were reduced to once a week. Unfortunately, this led to a repeated increase of TG level and twice-weekly regimen was reestablished with a decrease of TG but this time not below 11.3 mmol/L. After 33 weeks, despite sessions twice a week, TG levels started to exceed 22.6 mmol/L and last session was complicated by low blood flow. Despite this, overall treatment was successful in preventing acute pancreatitis attack.

We also documented no severe adverse effects. Plasma exchange was very well tolerated by our patient and also the fetus. To prevent iron deficiency anemia, iron supplements were given. Although there was a laboratory decrease in iron levels, the level of hemoglobin was maintained within the range of mild anemia without the need for transfusion therapy. While it has been theorized that when plasma is used as a replacement fluid it can be a source of lipoprotein lipase28, we used albumin as a replacement to avoid potential complications associated with transfusion therapy23. One study reported a modification of cardiac fetal rhythm and decrease in active fetal movements during TPE with improvement after a few hours24. Our patient was regularly examined by an obstetrician, 11 times in total and due to high risk of preeclampsia quantitative proteinuria was examined in weekly intervals.

Previous findings reported a percent decrease of serum TG levels after TPE session 66-70% (ref. 4,12,20). In our case, mean decrease of 33.27% is most likely due to the use of membrane as opposed to centrifugal method of apheresis, which is not available in our settings. Some articles report greater removal with centrifugation, because of the tendency of TG to clog the pores of the filters12,31.

CONCLUSION

Severe gestational hypertriglyceridemia, as one of the most common causes of non-biliary pancreatitis, poses a rare but serious problem during pregnancy. When medical nutrition therapy and other standardly used medical interventions are not able to sufficiently lower the TG levels, therapeutic plasma exchange may be considered. A few current published reports, including ours, support its use as a safe and efficient method not only in the treatment of ongoing acute pancreatitis but also as a preventive measure. However, more research is needed to establish reliable guidelines to ensure its highest efficiency.

ABBREVIATIONS

BMI, Body mass index; CPAP, of continuous positive airway pressure; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; TPE, Therapeutic plasma exchange; TG, Triglyceride.


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REFERENCES


