

Hypertriglyceridemia-induced pancreatitis in pregnancy: case review on the role of therapeutic plasma exchange

Sarah Ying Tse Tan¹, Swee Ping Teh², Manish Kaushik², Tze Tein Yong³, Shivani Durai³, Claudia Jong-Chie Tien⁴ and Daphne Su-Lyn Gardner¹

¹Department of Endocrinology, Singapore General Hospital, Singapore, ²Department of Renal Medicine, Singapore General Hospital, Singapore, ³Department of Obstetrics and Gynaecology, Singapore General Hospital, Singapore, and ⁴Department of Anaesthesiology and Surgical Intensive Care, Singapore General Hospital, Singapore

Correspondence
should be addressed
to S Y T Tan
Email
sarah.tan92@yahoo.com

Summary

Gestational hypertriglyceridemia-induced pancreatitis is associated with significant maternal and fetal morbidity and mortality. We report a case of gestational hypertriglyceridemia-induced pancreatitis in a primigravida at 31-weeks gestation, complicated by impending preterm labor and metabolic acidosis requiring hemodialysis. This was successfully managed with therapeutic plasma exchange (TPE), followed by i.v. insulin, low-fat diet, and omega-3. Triglyceride levels stabilized after TPE and the patient underwent an uncomplicated term delivery. In pregnancy, elevated estrogen and insulin resistance exacerbate hypertriglyceridemia. Management is challenging as risks and benefits of treatment options need to be weighed against fetal wellbeing. We discuss management options including a review of previous case reports detailing TPE use, dietary optimization, and delivery timing. This case emphasizes the importance of multidisciplinary care to optimize maternal and fetal outcomes.

Learning points:

- Gestational hypertriglyceridemia-induced pancreatitis has high morbidity.
- A multidisciplinary team approach is a key as maternal and fetal needs must be addressed.
- Rapid lowering of triglycerides is crucial and can be achieved successfully and safely with plasma exchange.
- A low-fat diet while ensuring adequate nutrition in pregnancy is important.
- Timing of delivery requires consideration of fetal maturity and risk of recurrent pancreatitis.

Background

Hypertriglyceridemia-induced pancreatitis is associated with significant morbidity and mortality. Its management in pregnancy is complex and often associated with poor fetal outcomes. We report the case of a primigravida at 31-weeks' gestation with no previous medical history who presented with hypertriglyceridemia-induced pancreatitis. The patient had impending preterm labor and required hemodialysis and therapeutic plasma exchange (TPE). We review the outcomes of previous

reports and considerations for TPE, discuss the etiology of hypertriglyceridemia in pregnancy, and subsequent management till delivery.

Case presentation

A 32-year-old primigravida presented with acute epigastric pain, vomiting, and fever at week 31 of gestation. Fetal movement was normal. The patient had no personal

nor known family medical history of lipid disorders and was not on medications. Antenatal history had been uneventful. Pre-pregnancy weight was 55 kg (BMI 22.3 kg/m²) and fasting plasma glucose (10 weeks gestation) was normal (3.7 mmol/L). Oral glucose tolerance test, HbA1c, and lipid panel had not been performed. The patient was febrile (T 38.3°C), tachycardic (HR 125 bpm), hypotensive (BP 98/59 mmHg), and tachypneic, with a tender epigastrium. There was no lipodystrophy, acanthosis nigricans nor eruptive xanthomas.

Investigation

A blood draw revealed a lipemic sample (Fig. 1A). Serum triglyceride levels were markedly elevated (>50 mmol/L), with metabolic acidosis (bicarbonate 13.4 mmol/L). Amylase and lipase levels were elevated (867 U/L and >600 U/L, respectively), consistent with acute pancreatitis. Serum bilirubin, calcium, glucose, and thyroid hormone levels were normal (Table 1).

Treatment

As the diagnosis of acute pancreatitis secondary to hypertriglyceridemia (modified Marshall score 3) was established, the patient was kept nil-per-os and given i.v. fluids. A few hours later, the patient developed uterine contractions suggesting impending preterm labor. Metabolic acidosis worsened (pH 7.25, bicarbonate 8.3 mmol/L) requiring initiation of dialysis. Betamethasone was administered for fetal lung maturation. Given the need to rapidly lower the triglyceride levels, and taking into account that Betamethasone was likely to exacerbate hypertriglyceridemia (increased triglyceride synthesis), TPE was initiated (Fig. 1B). As she was critically ill and potentially required emergency surgery, oral medications were not commenced yet.

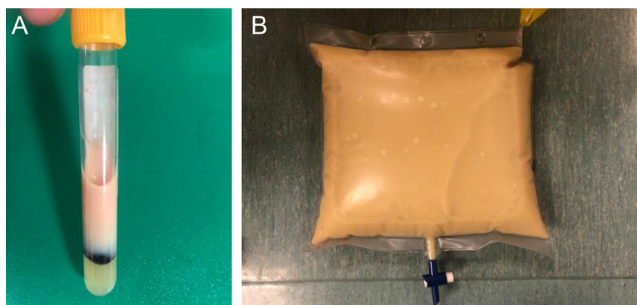


Figure 1
(A) Lipemic blood sample. (B) Lipemic plasma sample during TPE.

Table 1 Laboratory investigations on admission.

Laboratory test	Result	Reference range
Amylase, U/L	867	38–149
Lipase, U/L	>600	8–55
Triglycerides, mmol/L	>50	<1.7
Total cholesterol, mmol/L	37.36	<5.2
Venous glucose, mmol/L	4.8	3.9–11
Sodium, mmol/L	119	136–146
Potassium, mmol/L	3.0	3.6–5.0
Bicarbonate, mmol/L	13.4	19.0–29.0
Creatinine	UNS	37–75
Calcium, mmol/L	1.99	2.09–2.46
Phosphate, mmol/L	1.02	0.94–1.50
Magnesium, mmol/L	1.52	0.74–0.97
Ketones, mmol/L	3.5	0–0.6
Albumin, g/L	34	40–51
Bilirubin, µmol/L	8	7–32
AST, U/L	UNS	12–42
ALT, U/L	UNS	6–66
ALP, U/L	76	39–99
Hemoglobin, g/dL	10.5	12–16
White cell count, × 10 ⁹ /L	13.04	4–10
Platelets, × 10 ⁹ /L	274	140–440
HbA1c, %	6	
FT4, pmol/L	8.8	8.8–14.4
TSH, mIU/L	0.937	0.65–3.70

Abnormal values are indicated in bold.
UNS, unsuitable specimen.

One plasma volume (3.5L) was replaced with an equal volume of fresh frozen plasma (FFP), initially without anticoagulation as emergency cesarean section could have been required. However, the circuit filter clotted, and regional citrated anticoagulation was initiated. After one session of TPE, triglyceride levels fell to 31.29 mmol/L. Intravenous insulin infusion was continued with improvement in triglyceride levels (Fig. 2A). The patient had no further contractions, and hemodialysis was stopped the next day.

When the triglycerides fell to 12.39 mmol/L (day 4), i.v. insulin was stopped, and a very low-fat diet (<20 g fat/day) and omega-3 fatty acids were implemented. Capillary blood glucose readings were elevated (6–10 mmol/L), likely related to gestational diabetes and acute pancreatitis. Multiple daily insulin injections were commenced to achieve pre-prandial glucose targets of <5.5 mmol/L and 1-h post-prandial targets of <7.8 mmol/L (total daily dose 0.67 u/kg/day). The patient remained in a good medical state and was discharged after 12 days.

Outcome and follow-up

Post-discharge, triglyceride levels remained stable (7.19–9.12 mmol/L, Fig. 2B). However, due to the very low-fat

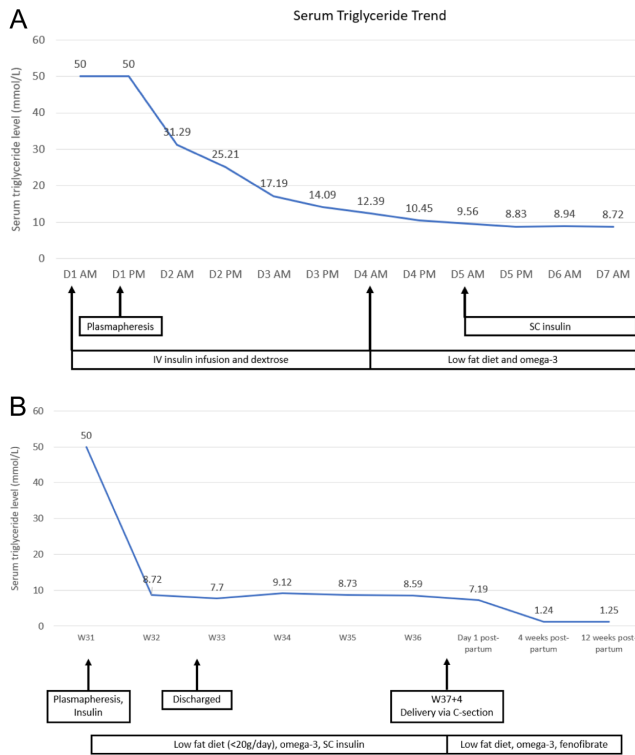


Figure 2
(A) Serum triglyceride trend inpatient. (B) Serum triglyceride trend outpatient.

intake, the patient struggled to meet caloric requirements. Between weeks 32–36, her weight fell from 65.4 to 60.7 kg. There was no fetal growth restriction detected throughout this period.

Labor was induced at week 37 and a cesarean section was eventually performed due to non-progression of labor. A healthy baby boy (3045 g, APGAR scores of 8 and 9) was delivered. Two days post-delivery, triglyceride levels fell to 7.27 mmol/L and blood glucose levels ranged 4.3–6.9 mmol/L without insulin. Despite encouragement, the patient decided not to breast-feed. Fenofibrate was started and the patient continued a low-fat diet and omega-3 fish oil. A month post-delivery, triglyceride levels fell to 1.24 mmol/L.

Discussion

Pathophysiology and etiology

Hypertriglyceridemia is related to increased availability or synthesis through the exogenous or endogenous pathways, decreased processing by lipoprotein lipase (LPL), and decreased hepatic clearance by the LDL receptor. The elevated estrogen levels in pregnancy enhance lipogenesis and suppress hepatic lipase activity,

while pregnancy-related insulin resistance contributes to increased lipolysis and decreased LPL activity (1). These parameters lead to raised triglyceride levels (two- to four-fold) in late gestation, especially in concurrent gestational diabetes (1).

Severe hypertriglyceridemia in pregnancy (triglycerides >11.2 mmol/L) is uncommon and usually points toward an underlying genetic abnormality for example, monogenic disorders in genes affecting LPL levels or activity (2). Polygenic inheritance of multiple genes results in more common but milder levels of hypertriglyceridemia. Secondary factors such as insulin resistance, hypothyroidism, and glucocorticoids also play an important role (3).

About 15–20% of the patients with triglycerides >11.2 mmol/L develop acute pancreatitis, related to the metabolism of excessive triglycerides by pancreatic lipase, leading to pancreatic cell injury and ischemia. Complication rates (peripancreatic collections, necrotizing pancreatitis) are twice as high in hypertriglyceridemia-induced pancreatitis (4). In pregnancy, hypertriglyceridemia-induced pancreatitis is associated with a higher risk of organ failure and intensive care support, and fetal loss, preterm labor, pre-eclampsia, and abruptio placentae (3, 4). The accumulation of lipids also increases the risk of fetal macrosomia resulting in pre-term delivery (5). Earlier diagnoses and management have decreased maternal and fetal mortality, with one report indicating a decrease in maternal and fetal mortality from 37 to 0%, and 60 to 3%, respectively (5).

Management

Acute setting

Hypertriglyceridemia-induced pancreatitis in pregnancy requires prompt management. Supportive measures and close monitoring for complications (pancreatic necrosis, adult respiratory distress syndrome, acute kidney injury, and systemic inflammatory response syndrome) should be conducted. Specifically, rapid lowering of triglyceride levels is crucial (6). Evidence for implementing this is currently limited to retrospective case reports with no clear guidelines available.

Therapeutic plasma exchange (TPE) TPE lowers triglyceride levels by rapidly removing triglycerides and chylomicrons and may improve outcomes by removing inflammatory markers and cytokines (6). Replacement with FFP has been postulated to replace deficient LPL or apolipoproteins, facilitating the degradation of triglycer-



Table 2 Case reports on the use of therapeutic plasma exchange for hypertriglyceridemia-induced acute pancreatitis in pregnancy.

Reference	Gestation week	Triglyceride level (mmol/L)	TPE details	Plasma processed	Replacement fluid	Anticoagulation	Number of sessions	Pregnancy outcome
(8)	5	25.1	NA	40 mL/kg body weight	FFP	Heparin 10 U/kg	3	Fetal loss
(17)	27	30.4	NA	40 mL/kg body weight	FFP	Heparin 10 U/kg	14 (8 + 6)	C-section at 34 weeks
(18)	31	109.9	Double filtration TPE	Filtered plasma volume 2.5 L/h	NA	NA	1	Intra uterine fetal death
(15)	35	35	NA	40 mL/kg body weight	FFP	30 mg/h nafamostat mesilate	1	Preterm delivery at 35 weeks
(9), n = 5	38	141.9	NA	NA	NA	NA	1 (after delivery)	Immediate C-section
(10)	32 (mean)	20.36 ± 7.41	Membrane plasma separation	40 mL/kg body weight	Albumin 5%	Heparin 750–1000 U/hr	1 to 3 session/patient	Four C-section; one termination
(19)	28	64.1	Centrifugal separation	40 mL/kg body weight	FFP	Heparin 10 U/kg	7	C-section at 38 weeks
(11)	22	20.9	Centrifugal separation	40 mL/kg body weight	FFP	Heparin 10 U/kg	2	C-section at 36 weeks
(20)	30	22.2	NA	2 L	Albumin 5%	NA	3	Abruption placenta; delivery at 33 weeks
(12)	24	18.56	Membrane plasma separation (re-use)	2 L	1.6 L Ringer's solution and 0.4 L albumin 20%	NA	13	Elective C-section at 26 weeks
(21)	25	NA	NA	2 L	Albumin 5%	NA	-3	Mother had ARDS; spontaneous delivery at 38 weeks.
(22)	9 (post-IVF)	111.2	NA	40 mL/kg	Crystalloid and albumin	Heparin 10 U/kg	4	Term delivery
(23)	28	30.04	NA	1.0 × plasma volume	5% albumin	Acid citrate dextrose	9	C-section at 35 weeks
(12)	33	87.5	NA	NA	NA	NA	3	Emergency C-section at 33rd week
(24), n = 39	33	87.1	Centrifugation	1.5 × plasma volume	5% albumin	Citrate anticoagulation	3 (2 + 1)	Delivery at 37 weeks
	>28	24.32 ± 6.59	NA	1.6–2.0 L	NA	NA	2–5	One fetal death; delivery outcomes not reported

NA, not available.



ides (6). However, due to a lack of randomized controlled trials, TPE is considered as category III therapeutic measure for hypertriglyceridemia-induced pancreatitis (7).

Table 2 summarizes the cases described involving the use of TPE in pregnancy-related hypertriglyceridemia-induced pancreatitis. TPE appears extremely effective in rapidly lowering triglyceride levels by 50–80% (8), even when hypertriglyceridemia is refractory to medical therapy (9). In a particular series, five out of ten individuals who underwent TPE had a lower incidence of systemic inflammatory response syndrome and length of hospitalization (10). Other reports concur describing a quick recovery over 3–4 days following TPE (11). However, even in the setting of TPE, complication rates were still high: of fifty-eight cases, four fetal deaths were reported. The majority of the patients required cesarean sections, and only four achieved term delivery. This highlights the critical nature of this condition and the need for a prompt and multi-pronged approach in achieving optimal maternal and fetal outcomes. Whilst TPE has been used to prevent pancreatitis in pregnant women with hypertriglyceridemia, its potential risks, and transient effect in lowering triglyceride with the possibility of rebound hypertriglyceridemia, limit its role in the acute setting (12, 13).

In conducting TPE, plasma volume estimation, replacement fluid choice, and anticoagulation need to be considered. The variable increase in plasma volume (20–150%, average 45%) in pregnancy confounds decisions on exchange volume (13). Both albumin and plasma could be used in replacement, with the latter having the theoretical benefit of providing LPL (7). It is currently unclear which anticoagulation is preferred. A retrospective study reported a lower mortality with citrate anticoagulation; however, heparin anticoagulation appears more commonly used in the case series below, with no clear signal of benefit or detriment (14) (Table 2).

Intravenous insulin Intravenous insulin therapy lowers triglyceride levels by activating LPL and increasing chylomicron degradation with an expected fall of 50–75% over 2–3 days (15). This is associated with shorter hospitalization stays and lower APACHE scores after 72 h of treatment (15). Its utility extends to non-diabetics, with frequent monitoring of electrolytes and a dextrose infusion to maintain euglycemia (16).

Heparin Continuous heparin infusions could lower triglyceride levels by releasing stored LPL from endothelial cells (2). This potential benefit must be weighed against

the risk of bleeding and hemorrhagic pancreatitis. Continuous heparin infusion may also deplete LPL, with rebound hypertriglyceridemia upon cessation (17). We refrained from using i.v. heparin infusion due to the potential bleeding risk during insertion of vascular catheters, and potential impending preterm labor.

Non-acute setting

Diet and pharmacotherapy Dietary modification remains the cornerstone of successful management. Total fat should be restricted to <20% of daily caloric intake. High glycemic index foods should be avoided since they enhance the hepatic synthesis of fatty acids. Low-fat diets pose a risk for essential fatty acid deficiency, and supplementation with oral omega-3 fatty acid should be prescribed as they are safe in pregnancy (2). At higher doses, these could reduce hepatic triglyceride synthesis and increase lipoprotein lipase activity, lowering serum triglyceride levels by 25–30%.

There are limited data on the use of fibrates and niacin after the first trimester (category C). Gemfibrozil may be considered in very severe hypertriglyceridemia from the second trimester (2). However, the onset of action is gradual, limiting its efficacy in the acute setting.

Conclusions

Hypertriglyceridemia-induced pancreatitis in pregnancy is a rare but potentially devastating condition associated with high maternal and fetal morbidity and mortality. A multidisciplinary approach is needed in supportive management and measures to reduce triglyceride levels rapidly. TPE is the quickest method and should be considered as first-line therapy. Maintaining a very low-fat diet to prevent recurrence of pancreatitis must be weighed against the need to achieve adequate maternal and fetal nutrition. Timing of delivery is individualized according to the risk of further episodes of pancreatitis vs fetal maturity.

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.

Author contribution statement

Y T S Tan was involved in conception, design and writing of manuscript. S P Teh and S Durai were involved in writing and critical review of manuscript. M Kaushik, T T Yong and C J C Tien were involved in conception, design and critical review of manuscript. Tien D S L Gardner was involved in conception, design, writing and critical review of manuscript

References

- Ghio A, Bertolotto A, Resi V, Volpe L & Di Cianni G. Triglyceride metabolism in pregnancy. *Advances in Clinical Chemistry* 2011 **55** 133–153. (<https://doi.org/10.1016/B978-0-12-387042-1.00007-1>)
- Wong B, Ooi TC & Keely E. Severe gestational hypertriglyceridemia: a practical approach for clinicians. *Obstetric Medicine* 2015 **8** 158–167. (<https://doi.org/10.1177/1753495X15594082>)
- Cruciat G, Nemeti G, Goideacu I, Anitan S & Florian A. Hypertriglyceridemia triggered acute pancreatitis in pregnancy – diagnostic approach, management and follow-up care. *Lipids in Health and Disease* 2020 **19** 2. (<https://doi.org/10.1186/s12944-019-1180-7>)
- Vipperla K, Somerville C, Furlan A, Koutroumpakis E, Saul M, Chennat J, Rabinovitz M, Whitcomb DC, Slivka A, Papachristou GI, et al. Clinical profile and natural course in a large cohort of patients with hypertriglyceridemia and pancreatitis. *Journal of Clinical Gastroenterology* 2017 **51** 77–85. (<https://doi.org/10.1097/MCG.0000000000000579>)
- Ducarme G, Maire F, Chatel P, Luton D & Hammel P. Acute pancreatitis during pregnancy: a review. *Journal of Perinatology* 2014 **34** 87–94. (<https://doi.org/10.1038/jp.2013.161>)
- Stefanutti C, Labbadia G & Morozzi C. Severe hypertriglyceridemia-related acute pancreatitis. *Therapeutic Apheresis and Dialysis* 2013 **17** 130–137. (<https://doi.org/10.1111/1744-9987.12008>)
- Padmanabhan A, Connelly-Smith L, Aquino N, Balogun RA, Klingel R, Meyer E, Pham HP, Schneiderman J, Witt V, Wu Y, et al. Guidelines on the use of therapeutic apheresis in clinical practice – evidence-based approach from the writing Committee of the American Society for Apheresis: the eighth special issue. *Journal of Clinical Apheresis* 2019 **34** 171–354. (<https://doi.org/10.1002/jca.21705>)
- Galán Carrillo I, Demelo-Rodríguez P, Rodríguez Ferrero ML & Anaya F. Double filtration plasmapheresis in the treatment of pancreatitis due to severe hypertriglyceridemia. *Journal of Clinical Lipidology* 2015 **9** 698–702. (<https://doi.org/10.1016/j.jacl.2015.07.004>)
- Altun D, Eren G, Cukurova Z, Hergünel O & Yasar L. An alternative treatment in hypertriglyceridemia-induced acute pancreatitis in pregnancy: plasmapheresis. *Journal of Anaesthesiology, Clinical Pharmacology* 2012 **28** 252–254. (<https://doi.org/10.4103/0970-9185.94913>)
- Huang C, Liu J, Lu Y, Fan J, Wang X, Liu J, Zhang W & Zeng Y. Clinical features and treatment of hypertriglyceridemia-induced acute pancreatitis during pregnancy: a retrospective study. *Journal of Clinical Apheresis* 2016 **31** 571–578. (<https://doi.org/10.1002/jca.21453>)
- Kandemir A & Coşkun A. Treatment of hypertriglyceridemia-induced acute pancreatitis with therapeutic plasma exchange in 2 pregnant patients. *Journal of Obstetrics and Gynaecology* 2019 **39** 702–704. (<https://doi.org/10.1080/01443615.2018.1553939>)
- Michalova R, Mankova A, Vnucak M, Mikulova S, Nehaj F, Raslova K, Dedinska I, Jezikova A, Makovicky P, Galajda P, et al. Therapeutic plasma exchange in secondary prevention of acute pancreatitis in pregnant patient with familial hyperchylomicronemia. *Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia* 2019 **163** 90–94. (<https://doi.org/10.5507/bp.2018.044>)
- Simmons SC, Dorn DP, Walton CM, Williams LA & Pham HP. Hypertriglyceridemia in pregnancy. *Transfusion* 2017 **57** 2824–2825. (<https://doi.org/10.1111/trf.14176>)
- Gubensek J, Buturovic-Ponikvar J, Romozi K & Ponikvar R. Factors affecting outcome in acute hypertriglyceridemic pancreatitis treated with plasma exchange: an observational cohort study. *PLoS ONE* 2014 **9** e102748. (<https://doi.org/10.1371/journal.pone.0102748>)
- Li J, Chen TR, Gong HL, Wan MH, Chen GY & Tang WF. Intensive insulin therapy in severe acute pancreatitis: a meta-analysis and systematic review. *West Indian Medical Journal* 2012 **61** 574–579.
- Gupta N, Ahmed S, Shaffer L, Cavens P & Blankstein J. Severe hypertriglyceridemia induced pancreatitis in pregnancy. *Case Reports in Obstetrics and Gynecology* 2014 **2014** 485493. (<https://doi.org/10.1155/2014/485493>)
- Watts GF, Cameron J, Henderson A & Richmond W. Lipoprotein lipase deficiency due to long-term heparinization presenting as severe hypertriglyceridaemia in pregnancy. *Postgraduate Medical Journal* 1991 **67** 1062–1064. (<https://doi.org/10.1136/pgmj.67.794.1062>)
- Goto S, Ookawara S & Tabei K. Effectiveness of Plasma Exchange for Acute Pancreatitis Induced by Hypertriglyceridemia During Pregnancy. *Therapeutic Apheresis Dialysis* 2016 **20** 98–99. (<https://doi.org/10.1111/1744-9987.12373>)
- Lim R, Rodger SJ & Hawkins TL-A. Presentation and management of acute hypertriglyceridemic pancreatitis in pregnancy: A case report. *Obstetric Medicine* 2015 **8** 200–203. (<https://doi.org/10.1177/1753495X15605697>)
- Perrone S, Brunelli R, Perrone G, et al. A successful term pregnancy with severe hypertriglyceridaemia and acute pancreatitis. Clinical management and review of the literature. *Atherosclerosis Supplements* 2019 **40** 117–121. (<https://doi.org/10.1016/j.atherosclerosisup.2019.08.032>)
- Reper P, Attou R, Gucciardo L, Gottignies P, Devriendt J & Massaut J. Early plasmapheresis as a successful treatment in hypertriglyceridemia-induced acute pancreatitis in first trimester pregnancy following in vitro fertilization. *European Journal of Obstetrics Gynecology and Reproductive Biology* 2014 **179** 257–258. (<https://doi.org/10.1016/j.ejogrb.2014.04.018>)
- Safi F, Toumeh A, Abuissa Qadan MA, Karaz R, AlAkdar B & Assaly R. Management of Familial Hypertriglyceridemia-Induced Pancreatitis During Pregnancy With Therapeutic Plasma Exchange: A Case Report and Review of Literature. *American Journal of Therapeutics* 2014 **21** e134–e136. (<https://doi.org/10.1097/MJT.0b013e31825b9e98>)
- Serpytis M, Karosas V, Tamosauskas R, et al. Hypertriglyceridemia-induced Acute Pancreatitis in Pregnancy. *Journal of the Pancreas* 2012 **13** 677–680. (<https://doi.org/10.6092/1590-8577/1148>)
- Zheng Y, Hu W, Wang J, Hu W & Liu C. Plasmapheresis for the treatment of hypertriglyceridemia-induced severe acute pancreatitis in pregnancy: it could be a good choice. *International Journal of Colorectal Disease* 2015 **30** 1443–1444. (<https://doi.org/10.1007/s00384-015-2137-6>)

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