Hypertriglyceridaemia in pregnancy: an unexpected diagnosis and its management

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Accepted 31 July 2022

SUMMARY

A woman in her 30s with gestational diabetes presented at 36 weeks' gestation with reduced fetal movements and diminishing insulin requirements. In view of her gestation, she was induced and incidentally found to have profound hyponatraemia. Further biochemical investigations confirmed severe hypertriglyceridaemia and hypercholesterolaemia. This raises the possibility of secondary causes such as familial dysbetalipoproteinemia and polygenetic hypertriglyceridaemia. She was successfully managed by aggressive dietary modification. This involved a supervised fast followed by a fat-free diet. A fenofibrate was proposed but declined due to our patient's wish to breastfeed. Management required considerable input from the multidisciplinary team. Treatment options to consider are aggressive dietary restriction of fat or the addition of a cholesterol-lowering medication, such as a fibrate. In refractory cases, a supervised fast may be required or, in cases where complications have arisen, apheresis. The patient and her baby made a good recovery with no long-lasting health implications.

BACKGROUND

During pregnancy, significant alterations to lipid homeostasis occur. Hormonally driven changes alter levels of circulating triglycerides (TG), fatty acids, cholesterol and phospholipids. The most profound plasma lipid change is in plasma TG levels, with a two- to three-fold increase by the third trimester.[1] More profound TG rises are seen in women with diabetes in pregnancy and in the context of pre-existing conditions, such as insulin resistance or familial combined hyperlipidaemia. Women with diabetes in pregnancy choosing inadvisably to follow a carbohydrate-restricted but high-fat diet, are likely to exacerbate hypertriglyceridaemia further. This can result in complications such as hypertriglyceridaemia-induced pancreatitis, hyperviscosity syndrome and pre-eclampsia.[1] Careful clinical consideration must be undertaken to balance maternal and fetal health to avoid devastating morbidity and mortality outcomes. Furthermore, there are no national guidelines regarding this condition, and so we hope our experience will provide invaluable guidance to colleagues and add to the evidence base of this rare condition.

CASE PRESENTATION

An Asian woman in her 30s; gravida 2, para 1, was referred to the antenatal diabetic clinic at 9 weeks' gestation. She was offered early screening due to previous gestational diabetes. She was not known to have any lipid abnormalities in her previous pregnancy. It was noted she had impaired fasting blood glucose and a glycated hemoglobin (HbA1c) of 41 mmol/mol. This is diagnostic for gestational diabetes, as per new guidance for maternal medicine services during the coronavirus pandemic.[2] There was no family history of lipid disorders, only type 2 diabetes. She had no other relevant medical history, was on no regular medication and did not smoke cigarettes or consume alcohol.

Her self-monitored blood glucose (SMBG) levels were elevated, and so metformin 500 mg once a day was commenced to optimise gestational glycaemic control. Advice was provided about dietary management for gestational diabetes. She followed the Gestational Diabetes UK dietary advice by reducing refined carbohydrates while increasing intake of food rich in fat and protein. This was poorly tolerated due to hyperemesis gravidarum. Her SMBG remained elevated and basal insulin was introduced at 12 weeks' gestation. Subsequently, this was optimised to a basal bolus insulin regimen. Her insulin requirement increased rapidly, peaking at 40 units daily by 29 weeks' gestation. Despite this, fetal growth was normal on ultrasound at 28, 32 and 36 weeks.

She was planning a vaginal birth and was due to be induced at 38 weeks' gestation. However, at 36+1 weeks' gestation, the patient presented with reduced fetal movements and a reduction in her insulin requirement. Her daily insulin dose had fallen steadily from 30 weeks' gestation. It had fallen to such an extent that she had no insulin requirement for 48 hours prior to this presentation. Her bedside observations were unremarkable; respiratory rate was 16, oxygen saturation was 97% on room air, heart rate was 98, blood pressure 157/94 and her tympanic temperature was 36.4°C. She had a normal clinical examination. There was no eruptive cutaneous xanthomas, no orange palmar crease xanthoma and no hepatosplenomegaly. Fetal wellbeing was satisfactory with the cardiotocogram. Due to the reduced fetal movements and significant reduction in insulin requirement, she was offered hospital admission to the labour ward for induction in view of her gestation.

She received antenatal glucocorticoids, underwent artificial rupture of membranes and oxytocin administration for ongoing induction of labour. She was offered a balloon catheter induction 24 hours after the second glucocorticoid injection. She only needed to use 2 units of Levemir after the glucocorticoid administration to maintain a normal capillary blood glucose range.

To cite: Barclay K, Koysombat K, Padmagirison R, *et al*. *BMJ Case Rep* 2022;**15**:e249000. doi:10.1136/bcr-2022-249000

Table 1 Laboratory results 2 years prior compared with current presentation

Laboratory test (unit)	Results 2 years prior	Current presentation	Reference range
Serum sodium (mmol/L)	139	120	133–146
Serum potassium (mmol/L)	4.5	3.7	3.50–5.30
Serum urea (mmol/L)	4.7	3.0	2.50–7.80
Serum creatinine (µmol/L)	60	44	45.00–84.00
Serum cholesterol (mmol/L)	4.1	34.6	0.00–4.90
Serum HDL cholesterol (mmol/L)	0.9	<0.08	1.21–9999.00
Serum triglycerides (mmol/L)	1.01	>50.00	0.00–1.69
Serum cholesterol/HDL ratio	4.5	311.3	
Serum non-HDL cholesterol (mmol/L)	3.2	24.82	
Plasma fasting glucose (mmol/L)	5.3	5.2	4.10–6.00
Serum 09:00 cortisol (nmol/L)		711	
Serum thyroid-stimulating hormone (mU/L)		2.11	0.27–4.2
Serum free T4 (pmol/L)		10.4	0.6–2.5
Serum osmolality (mmol/kg)		288	275–295
Random urine osmolality (mmol/kg)		739	40–1400
Urine sodium (mmol/L)		129.9	

HDL, high-density lipoprotein.

INVESTIGATIONS

Unexpectedly during labour, electrolytes revealed severe hyponatraemia of 120 mmol/L. The serum looked lipemic. This was noted for more than two samples. Inconsistently, a venous blood gas revealed a normal sodium. The patient remained asymptomatic of hyponatraemia. Her case was referred to the endocrinology and metabolic medicine teams. Furthermore, they advised carrying out detailed biochemical investigations into the cause of hyponatraemia, paying particular interest to the lipid profile. Her biochemistry is outlined in table 1 and is compared with 2 years prior to this event.

We note serum cholesterol was markedly elevated at 34.6 mmol/L (reference range (RR) 0.30–1.80 mmol/L) and TG >50 mmol/L (RR 0.3–1.8 mmol/L).

The conclusions drawn from table 1 are that the patient had an acute severe mixed hyperlipaemia. A diagnosis of severe gestational hypertriglyceridaemia was made and pseudohyponatraemia secondary to the severe dyslipidaemia. Hypertriglyceridaemia in pregnancy can be a first sign of familial dysbetalipoproteinemia (FD) or polygenetic hypertriglyceridaemia. Importantly, her amylase level was normal at 30 U/L (RR 30–118 U/L). Following this, an ultrasound of the abdomen was carried out which showed fatty liver infiltration but no signs of acute pancreatitis.

She was referred to the lipid clinic for consideration of apolipoprotein E (ApoE) genotyping. This was in view of the lipid phenotype, as pregnancy can evoke FD in patients who have genetic susceptibility. However, with lifestyle modifications, her serum monitoring post partum revealed a normal lipid profile and glucose levels were within range.

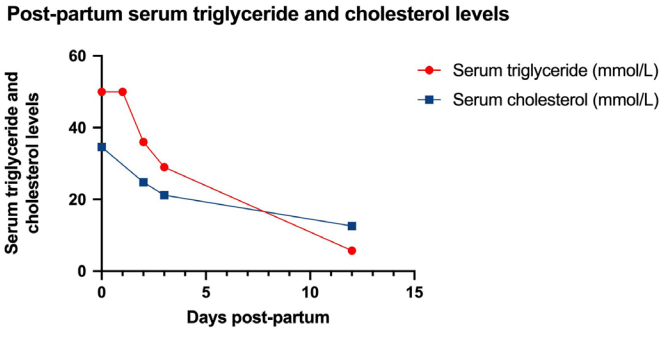

Figure 1 Serum triglyceride and cholesterol levels from delivery to day 12 post partum with diet modification.

OUTCOME AND FOLLOW-UP

After 48 hours of fasting, serum cholesterol and TG levels fell to 24.8 mmol/L and 36.6 mmol/L, respectively. A fat-free diet was commenced as per the recommendation from the diabetic team and dietitian. With continued aggressive dietary modification, her lipid profile drastically decreased. By day 12 post partum, serum cholesterol was 12.6 mmol/L and fasting TG 5.74 mmol/L (figure 1).

A fenofibrate was recommended but declined by the patient due to her wish to breastfeed.

Total inpatient stay was 11 days with conservative management. However, the postnatal period was complicated with maternal anaemia and suspected sepsis. She was treated with a blood transfusion and antibiotics as per the hospital policy which may have contributed to a prolonged hospital stay.

The baby's birth weight was 3.566 kg which placed the baby in the 76th centile. There were no concerns regarding the baby's health. The baby was breastfed from birth and had formula feed to ensure adequate neonatal feed was achieved.

At 6 weeks post-discharge, the patient had a normal serum lipid profile and blood glucose levels within normal range. Given this reassurance, the patient reintroduced a normal diet into her lifestyle. At 6 months, she was followed up in the lipid clinic. Her lipid profile remained unremarkable and SMBG levels were controlled. She was discharged from follow-up and did not require any further treatment. It was advised there is a high risk that severe hypertriglyceridaemia could recur in subsequent pregnancies and that she should inform a health professional before attempting to conceive. However, we note our patient was not planning any further pregnancies.

DISCUSSION

Hormonal changes physiologically increase plasma TG levels in pregnancy, particularly in the second and third trimesters. As progesterone increases during the first trimester, appetite is increased which results in weight gain and maternal fat deposition.[3] During the second and third trimesters, oestrogen and human placental lactogen levels increase resulting in insulin resistance, increased lipogenesis and increased TG-rich lipoprotein secretion. These metabolic changes are usually tolerated well and do not result in adverse clinical outcomes.[4]

In addition to the hormonally driven impact of pregnancy on lipid homeostasis causing a moderate increase in plasma TG level, women with gestational diabetes have significantly elevated plasma TG levels compared with those without.[5]

Severe gestational hypertriglyceridaemia is defined as a plasma TG exceeding 11.4 mmol/L, a level which is associated with increased risk of pancreatitis.[6] Patients who develop severe gestational hypertriglyceridaemia often have predisposing genetic susceptibilities in the TG metabolism pathways. This is either through increased TG production, ineffective lipolysis or decreased hepatic clearance of remnants.[1] This applies to our case and certain pre-existing genetic traits may render a pregnant woman susceptible to development of severe

hypertriglyceridaemia, especially in the third trimester. Genetic variants can be monogenetic or multigenetic. Monogenetic causes such a homozygous mutation in lipoprotein lipase (LPL) gene which is responsible for impaired LPL activity and ApoE gene polymorphism can be implicated in the causation of gestational hypertriglyceridaemia.[7]

This raises the possibility of FD. As in FD, there is a decreased hepatic clearance of remnants which is a contributing factor associated with ApoE2/E2 genotype.[6] The presence of secondary risk factors such as diabetes is generally required for the disease to manifest.[8]

Furthermore, there can be a polygenetic component to hypertriglyceridaemia. The cumulative effect of multiple genetic variants can impact TG levels. This can result in an increase in TG-increasing allele load and thus higher levels of TG. This is also impacted by secondary causes such as fatty liver disease and diabetes.[8]

We have not yet identified such genetic traits in our case, but wish to investigate this further.

Secondary risk factors include diabetes mellitus (particularly with suboptimal control), hypothyroidism, nephrotic syndrome, alcohol intake and the use of medications such as glucocorticoids, beta-blockers and protease inhibitors.[6] There are also rarer secondary causes such as myeloma, autoantibodies and partial lipodystrophies which need to be considered.[9]

A diminishing insulin requirement in a pregnant woman with diabetes can be indicative of placental insufficiency.[10] However, as our patient's baby was born within normal centiles, there was no evidence of placental insufficiency. We deduce that the reduction in insulin requirement was due to a falsely low capillary blood glucose reading caused by hypertriglyceridaemia. High TG levels take up volume decreasing the amount of glucose in the capillary volume.[11] The severe hyponatraemia which directed us to the diagnosis was explained by the lipemic blood specimen resulting in pseudohyponatraemia.

The management of severe gestational hypertriglyceridaemia is complex. As it is a rare condition, there are no published guidelines outlining management. A multidisciplinary approach is needed with collaboration from obstetrics, endocrinology, metabolic medicine and dietetics. This is recognised as the foundation for successful management.[6 12] The aim is to safely lower plasma TG levels and avoid maternal and fetal complications, without compromising their nutritional demands. Maternal complications include hypertriglyceridaemia-induced pancreatitis (affects 15%–20% of patients with severe gestational hypertriglyceridaemia), hyperviscosity syndrome, pre-eclampsia and increased risk of hyperlipoproteinaemia in subsequent pregnancies.[12] Fetal complications include macrosomia, preterm labour, prematurity and in-utero death.[6] These complications may be averted with prompt recognition and aggressive treatment.

Strict diabetic control is essential to prevent adverse maternal and fetal outcomes such as pre-eclampsia, polyhydramnios, macrosomia and neonatal intensive care unit admission.[13] Women should be counselled to restrict their consumption of high glycaemic index foods including refined sugar and high-fructose beverages. Total daily fat should be less than 20% of total caloric intake but may require further restriction depending on TG levels. Dietary restriction is very effective in lowering plasma TG by reducing the substrate for TG synthesis. Adequate essential fatty acid intake is required for both maternal and fetal well-being. Preterm labour, fetal growth restriction and impaired neural and retinal development may result from essential fatty acid deficiencies.[6] This can be addressed by the prescription of omega-3-esters, serving also to lower TG levels.

Fibrates and niacin both offer gradual reduction in plasma TG levels. However, in the acute setting a more rapid reduction may be desired. The therapeutic doses of niacin required to lower TG levels significantly has only been studied in non-pregnant patients. Fibrates may be considered in women after the first trimester, if unresponsive to dietary change and omega-3 fatty acids. Niacin is known to be excreted in breastmilk and it is unclear if fibrates are excreted in breastmilk.[6] Therefore, this needs to be carefully considered in the context of ongoing treatment and breastfeeding.

Women who remain refractory to treatment may require admission for a supervised fast together with intravenous 5% dextrose or parenteral nutrition. It has been hypothesised that intravenous feeding may have an attenuated TG raising effect compared with enteral carbohydrate intake.[6] Apheresis may be considered in severe gestational hypertriglyceridaemia complicated by pancreatitis or as a bridge to imminent delivery. Apheresis works by reducing TG levels and inflammatory cytokines, and the replacement plasma replaces deficient LPL or apolipoproteins and consumes protease inhibitors.[14] Complications such as rebound hypertriglyceridaemia, catheter line infection and thrombosis, and fetal deaths have been reported.[15]

Intravenous insulin is useful in patients with hyperglycaemia as improved glycaemic control increases LPL activity through increased LPL activation and reduction of LPL inhibition which occurs in the hyperglycaemic state.[6]

In our case, the diagnosis of severe hypertriglyceridaemia was made at near term following an induced labour. Therefore, fasting followed by a fat-restricted diet did not impact the health of the unborn child. Universal screening for gestation hypertriglyceridaemia is not undertaken at present. Therefore, it is imperative that women at risk of this condition are identified. As

Patient's perspective

My high lipid reading was first noted when I was in labour. I wasn't told about it until after the baby was born which helped in avoiding a stressful situation in the labour room. I was not as anxious in the beginning as I would have been pre-delivery and I wasn't experiencing any symptoms at all. But once I was put on fasting for longer hours and the post partum hormones kicked in, I started feeling rather anxious and sad. I have always been a foodie who enjoys eating everything. Hence the thought of having diet restrictions big time was really discouraging. The staff was very supportive and accommodating especially when they saw that I wasn't taking it well. Since my elder son couldn't come in the hospital premises due to covid restrictions, that only made my emotional state worse. However when I learnt from the daily tests that my lipid profile is coming down without any medical intervention, I started to feel less and less anxious! Much gratitude to the doctors for all the support I was given during the challenging times!

Learning points

- Gestational-induced hypertriglyceridaemia is rare but has a high morbidity.
- A multidisciplinary team approach is required to optimise maternal and fetal health.
- A low-fat diet alone has a significant role in improving the lipid profile in pregnant patients.

this condition is rare, our recommendation would be to monitor for pregnancy-related hypertriglyceridaemia in those with pre-pregnancy fasting TG levels greater than 4 mmol/L. In women in whom the fasting lipid profile is previously unknown, triggers for a lipid profile determination to detect elevated non-pregnant TG greater than 4 mmol/L would include; a family history of high TG, features of metabolic syndrome (such as obesity, dysglycaemia or hypertension) or a history of non-gallstone pancreatitis.[12] This would allow prompt monitoring and early intervention to avoid maternal and fetal complications. Management options should be tailored to individuals. For example, we had to consider our patient's wishes regarding breastfeeding with safe and appropriate management options. It is important this is supported by a multidisciplinary team. Further research is needed to address if a temporary low-fat diet with essential fatty acid supplementation has any impact on fetal health, and to explore the relationship between maternal serum TG level and the timing for induction and delivery for these pregnancies.

Acknowledgements The authors would like to thank Dr Adie Viljeon for his contribution to the patient's care.

Contributors KB and KK prepared the manuscript and performed literature review. RP and FK provided guidance and edited the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

REFERENCES

1 Kleess LE, Janicic N. Severe hypertriglyceridemia in pregnancy: a case report and review of the literature. *AACE Clin Case Rep* 2019;5:e99–103.
2 Guidance for maternal medicine services in the coronavirus (COVID-19) pandemic [Internet], 2020. Available: https://www.rcog.org.uk/guidance/coronavirus-covid-19-pregnancy-and-women-s-health/optimising-maternity-services-in-coronavirus-covid-19-pandemic/ [Accessed cited 9 June 2022].
3 Herrera E. Lipid metabolism in pregnancy and its consequences in the fetus and newborn. *Endocrine*2002;19.
4 Basaran A. Pregnancy-Induced hyperlipoproteinemia: review of the literature. *Reprod Sci* 2009;16:431–7.
5 Ryckman K, Spracklen C, Smith C, *et al*. Maternal lipid levels during pregnancy and gestational diabetes: a systematic review and meta-analysis. *BJOG: An International Journal of Obstetrics & Gynaecology* 2015;122:643–51.
6 Wong B, Ooi T, Keely E. Severe gestational hypertriglyceridemia: a practical approach for clinicians. *Obstetric Medicine* 2015;8:158–67.
7 Xie S, Chen T, Huang X, *et al*. Genetic variants associated with gestational hypertriglyceridemia and pancreatitis. *Plos One* 2015;10:e0129488.
8 Carrasquilla G, Christiansen M, Kilpeläinen T. The genetic basis of hypertriglyceridemia. *Current Atherosclerosis Reports* 2021;23.
9 Benuck I, Wilson D, McNeal C. Secondary Hypertriglyceridemia [Internet]. Ncbi.nlm.nih.gov, 2022. Available: https://www.ncbi.nlm.nih.gov/books/NBK395574/ [Accessed cited 27 July 2022].
10 Prior A, Jain V. Implications of decreasing insulin requirements for diabetes in pregnancy. *Obstetrics & Gynecology* 2020;135:42S.
11 Ginsberg BH. Factors affecting blood glucose monitoring: sources of errors in measurement. *J Diabetes Sci Technol* 2009;3:903–13.
12 Goldberg AS, Hegele RA. Severe hypertriglyceridemia in pregnancy. *The Journal of Clinical Endocrinology & Metabolism* 2012;97:2589–96.
13 Almalki M, Buhary B, Almohareb O, *et al*. Glycemic control and pregnancy outcomes in patients with diabetes in pregnancy: a retrospective study. *Indian Journal of Endocrinology and Metabolism* 2016;20:481.
14 Yeh J-H, Chen J-H, Chiu H-C. Plasmapheresis for hyperlipidemic pancreatitis. *J Clin Apher* 2003;18:181–5.
15 Tan SYT, Teh SP, Kaushik M, *et al*. Hypertriglyceridemia-induced pancreatitis in pregnancy: case review on the role of therapeutic plasma exchange. *Endocrinol Diabetes Metab Case Rep* 2021;2021. doi:10.1530/EDM-21-0017. [Epub ahead of print: 01 05 2021].