Management of adult hypertriglyceridemia & hyperlipidemia in pregnancy

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Objectives

- Outline the typical presentation for a patient with hypertriglyceridemia.
- Describe the recommended management of hypertriglyceridemia.
- Explain the interprofessional team strategies for improving care coordination and communication regarding the management of patients with hypertriglyceridemia.

Introduction

- Multifactorial
- Combination of genetic and factors and other causes of increased production and or impaired clearance of triglyceride-rich lipoproteins (TRLP)s.
- Lifestyle change and pharmacotherapy in addition to evaluation of underlying etiology.

Importance

- Reducing ASCVD risk: It is not established. Also, LDL-C levels may underrepresent cardiovascular risk in patients with hypertriglyceridemia. High TG levels are associated with small, dense cholesterol-depleted LDL particles that may not be captured by LDL-C measurement. **Non-high-density lipoprotein cholesterol** (non-HDL-C) and **apolipoprotein B concentrations** are better measures of the excess concentrations of atherogenic lipoproteins in patients with **moderate and severe hypertriglyceridemia**
- Pancreatitis

1. Simons-Linares CR, Jang S, Sanaka M, Bhatt A, Lopez R, Vargo J, Stevens T, Chahal P. The triad of diabetes ketoacidosis, hypertriglyceridemia and acute pancreatitis. How does it affect mortality and morbidity?: A 10-year analysis of the National Inpatient Sample. Medicine (Baltimore). 2019 Feb;98(7):e14378.
2. Sniderman AD, Couture P, Martin SS, DeGraaf J, Lawler PR, Cromwell WC, Wilkins JT, Thanassoulis G. Hypertriglyceridemia and cardiovascular risk: a cautionary note about metabolic confounding. J Lipid Res. 2018 Jul;59(7):1266-1275.
3. Peng J, Luo F, Ruan G, Peng R, Li X. Hypertriglyceridemia and atherosclerosis. Lipids Health Dis. 2017 Dec 06;16(1):233.
4. Reiner Ž. Hypertriglyceridaemia and risk of coronary artery disease. Nat Rev Cardiol. 2017 Jul;14(7):401-411.

Etiology

- Familial hypertriglyceridemia (excess VLDL but normal cholesterol) and Familial combined hyperlipidemia (polymorphisms of apolipoprotein C-II (apoC-II), apolipoprotein C-III (apoC-III), etc.) present predominantly with HTG.
- Lipoprotein lipase deficiency, Apolipoprotein C-II deficiency, Apolipoprotein AV deficiency, and dysbetalipoproteinemia are examples of genetic syndromes that present with chylomicronemia.

1. Schaefer EJ, Geller AS, Endress G. The biochemical and genetic diagnosis of lipid disorders. Curr Opin Lipidol. 2019 Apr;30(2):56-62. [PubMed]
2. Rygiel K. Hypertriglyceridemia - Common Causes, Prevention and Treatment Strategies. Curr Cardiol Rev. 2018 Mar 14;14(1):67-76.

Etiology

- Secondary causes of HTG include certain **medical conditions**, **drugs**, and **dietary** causes. **Obesity**, **metabolic syndrome**, **Diabetes mellitus** type 2, **hypothyroidism**, **Cushing's** syndrome, **CKD**, **HIV**, **pregnancy**, and some **autoimmune** conditions such as **SLE** have been associated with HTG.

1. Schaefer EJ, Geller AS, Endress G. The biochemical and genetic diagnosis of lipid disorders. Curr Opin Lipidol. 2019 Apr;30(2):56-62. [PubMed]
2. Rygiel K. Hypertriglyceridemia - Common Causes, Prevention and Treatment Strategies. Curr Cardiol Rev. 2018 Mar 14;14(1):67-76.

Etiology

- Medications that cause HTG include **thiazides**, **beta-blockers**, oral estrogens, **tamoxifen**, **OCPs**, **anti-retroviral protease inhibitors**, **atypical antipsychotics**, **isotretinoin**, **corticosteroids**, **bile acid-binding resins**, and **immunosuppressive** agents such as **sirolimus**.
- Dietary causes of HTG include excessive **alcohol** intake and foods rich in **saturated fat** or with a **high glycemic index**.

1. Schaefer EJ, Geller AS, Endress G. The biochemical and genetic diagnosis of lipid disorders. Curr Opin Lipidol. 2019 Apr;30(2):56-62. [PubMed]
2. Rygiel K. Hypertriglyceridemia - Common Causes, Prevention and Treatment Strategies. Curr Cardiol Rev. 2018 Mar 14;14(1):67-76.

Epidemiology

- Serum triglycerides are usually **higher in m**en than in women, especially until 70 years of age.
- The levels **increase with age** in both genders.
- The prevalence of hypertriglyceridemia is increasing among youth and adolescents due to increasing rates of **obesity** and **Diabetes mell**itus.
- The prevalence of hypertriglyceridemia was about 42% in people aged 60 years or older. The triglyceride levels were very high (>500 mg/dL) in about 2% of the subjects.

Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S., American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism. Council on Arteriosclerosis, Thrombosis and Vascular Biology. Council on Cardiovascular Nursing. Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011 May 24;123(20):2292-333

Classification

HTG is classified into

- **Normal – <150 mg/dL (<1.7 mmol/L)**
- **Moderate hypertriglyceridemia – 150 to 499 mg/dL (1.7 to 5.6 mmol/L)**
- **Moderate to severe hypertriglyceridemia – 500 to 999 mg/dL (5.65 to 11.3 mmol/L)**
- **Severe hypertriglyceridemia – ≥1000 mg/dL (≥11.3 mmol/L)**

1. Rygiel K. Hypertriglyceridemia - Common Causes, Prevention and Treatment Strategies. Curr Cardiol Rev. 2018 Mar 14;14(1):67-76.

Indication of treatment

4 to 12 weeks time

COR	LOE	RECOMMENDATIONS
I	B-NR	1. In adults 20 years of age or older with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175 to 499 mg/dL [2.0 to 5.6 mmol/L]), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes mellitus, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that increase triglycerides (S4.5.2-1).
IIa	B-R	2. In adults 40 to 75 years of age with moderate or severe hypertriglyceridemia and ASCVD risk of 7.5% or higher, it is reasonable to reevaluate ASCVD risk after lifestyle and secondary factors are addressed and to consider a persistently elevated triglyceride level as a factor favoring initiation or intensification of statin therapy (see Section 4.4.2.) (S4.5.2-2–S4.5.2-6).
IIa	B-R	3. In adults 40 to 75 years of age with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.6 mmol/L]) and ASCVD risk of 7.5% or higher, it is reasonable to address reversible causes of high triglyceride and to initiate statin therapy (S4.5.2-3–S4.5.2-5, S4.5.2-7, S4.5.2-8).
IIa	B-NR	4. In adults with severe hypertriglyceridemia (fasting triglycerides ≥500 mg/dL [≥5.7 mmol/L]), and especially fasting triglycerides ≥1,000 mg/dL (11.3 mmol/L)), it is reasonable to identify and address other causes of hypertriglyceridemia), and if triglycerides are persistently elevated or increasing, to further reduce triglycerides by implementation of a very low-fat diet, avoidance of refined carbohydrates and alcohol, consumption of omega-3 fatty acids, and, if necessary to prevent acute pancreatitis, fibrate therapy (S4.5.2-7, S4.5.2-9).

Pharmacotherapy

- **Statins**

- Statins lower triglyceride by about **10% - 30%** but in a dose-dependent manner.
- Statins are used as monotherapy in triglyceride levels of more than 500 m/dL when indicated to decrease cardiovascular risk.
- Ezetimibe can reduce TGL by about **5-10%.**
- A couple of trials (IMPROVE-IT and PRECISE IVUS) have shown that a combination of statin and ezetimibe has shown cardiovascular benefits. However, it should be remembered that neither statins nor ezetimibe has significant effects on TGL reduction, especially in high and very severe HTG.

Miller M, Stone NJ, Ballantyne C, Bittner V, Criqui MH, Ginsberg HN, Goldberg AC, Howard WJ, Jacobson MS, Kris-Etherton PM, Lennie TA, Levi M, Mazzone T, Pennathur S., American Heart Association Clinical Lipidology, Thrombosis, and Prevention Committee of the Council on Nutrition, Physical Activity, and Metabolism. Council on Arteriosclerosis, Thrombosis and Vascular Biology. Council on Cardiovascular Nursing. Council on the Kidney in Cardiovascular Disease. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011 May 24;123(20):2292-333

Pharmacotherapy

- **Omega-3 fatty acids (OM3FA)**
  - FDA approved for the treatment of severe and very severe hypertriglyceridemia (**greater than 1000 mg/dL**).
  - OMF3FA reduces triglycerides by **20% - 50%** at a dosage of 3 g to 4 g/day. Most OM3FA contain (EPA) and (DHA).
  - Studies have shown that the treatment of higher baseline triglycerides with OM3FA is associated with greater triglyceride lowering.
  - The effects of OM3FA on triglyceride lowering is **dose-related,** and the fact that various nonprescription OM3FA medications contain variable amounts of EPA and DHA, attention must be paid to the constituents in the selection of omega-3 fatty acids.

Choice of agent

- Marine-derived omega-3 fatty acid preparations contain omega-3-acid ethyl esters eicosapentaenoic acid (EPA) with or without docosahexaenoic acid (DHA).
- The recommended prescription omega fatty acid preparations differ from many fish oil supplements which contain only 30 to 50 percent omega-3 fatty acids and are taken at low doses. By comparison, the commercial preparation Vascepa contains more than 95 percent icosapent ethyl.

Choice of agent

- The dose of icosapent ethyl (Vascepa, which contains only the ethyl ester of EPA) is 2 g twice per day with meals. The icosapent ethyl product is ≥96 percent EPA so there is 3.8 g EPA per 4 g dose.

- The dose of omega-3 fatty acid ethyl esters (EPA+DHA) in generic or brand (Lovaza) form is 4 g once per day or 2 g twice per day with food. Lovaza contains 425 mg EPA and 345 mg DHA per 1000 mg capsule, so there is 3.1 g EPA+DHA per 4 g dose.

Pharmacotherapy

- **Omega-3 fatty acids (OM3FA)**
  - **Gastrointestinal discomfort and fish-like taste** are the limiting factors with high doses of nonprescription OM3FA.
  - In such cases, switching to FDA-approved prescription OM3FA may be helpful.
  - OM3FA has been shown to be associated with **increased conversion of VLDL to LDL**, thereby increasing levels of low-density lipoprotein cholesterol (LDL-C), but this effect has not been shown with the EPA-only prescription products.
  - However, so far, no studies have demonstrated cardiovascular disease benefit in hypertriglyceridemia with high dose OM3FA. In recent trials that lowering concomitant use of OM3FA with statins has failed to demonstrate a reduction in cardiovascular disease risk in spite of TGL lowering effects.

Pharmacotherapy

- **Fibrates**
  - A **30% to 50%** reduction with a concomitant **increase in HDL-C.**
  - A decrease in VLDL production, an increase in fatty acid oxidation, an increase in triglyceride catabolism, increase in LpL synthesis, and reduction in apoC-III.
  - Fenofibrate: cap 100 or 200 mg
  - Gemfibrozile: cap 300 and tab 450 mg; 600 mg BD 30 minutes before breakfast and dinner

Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AF., Endocrine society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012 Sep;97(9):2969-89.

Pharmacotherapy

- **Fibrates**

I. Since fibrates are largely excreted through **kidneys**, so, dose adjustment is necessary for patients with decreased renal function.

II. Fibrates are contraindicated in patients with the hepato-biliary disease. Fenofibrate is associated with a lower risk of myositis as compared to gemfibrozil and is the preferred agent among the two in patients already on statins. (glucuronidation of statin is inhibited)

III. Due to its protein binding nature, fenofibrate has interactions with other medications.

IV. Patients on fibrates and warfarin require close monitoring due to potential interactions. (30% warfarin dose reduction)

Berglund L, Brunzell JD, Goldberg AC, Goldberg IJ, Sacks F, Murad MH, Stalenhoef AF., Endocrine society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012 Sep;97(9):2969-89.

Treatment goal

- **Fibrates**
  I. A response to fibrates is seen as early as two weeks into therapy, with a maximal effect in six to eight weeks
  II. The goals of fibrate therapy are to reduce the triglyceride levels to less than **200 mg/dL** to decrease **cardiovascular disease risk**, as has been demonstrated in studies and trials.
  III. Pancreatitis: Evidence is lacking on the impact of fibrate therapy on the risk of pancreatitis in patients
  IV. with moderate to severe hypertriglyceridemia, as the available evidence is **largely limited to patients with lower TG levels.**
  V. Other benefits include the reduction of diabetic microvascular complications such as retinopathy and albuminuria.

Ruiz-García A, Arranz-Martínez E, Morón-Merchante I, Pascual-Fuster V, Tamarit JJ, Trias-Villagut F, Pintó-Sala X, Ascaso JF., Grupo de Diabetes de la Sociedad Española de Arteriosclerosis. Consensus document of the Spanish Society of Arteriosclerosis (SEA) for the prevention and treatment of cardiovascular disease in type 2 diabetes mellitus. Clin Investig Arterioscler. 2018 Jul;30 Suppl 1:1-19

Pharmacotherapy

- **Niacin:** It is no longer recommended except if not able to achieve desired response or intolerance to other therapy.

- Niacin has two formulations - **immediate release and extended-release**. Niacin reduces triglycerides by about 10% - 30%, while it increases.
- HDL-C by 10-40% and lowers LDL-C by 5-20%.
- Niacin decreases triglyceride synthesis and lipolysis.
- Clinical trials have **not demonstrated any cardiovascular disease benefit** of niacin in combination with statins, thereby resulting in decreased use of niacin.
- Among the side effects of niacin, flushing is common and can be reduced by concomitant administration of uncoated aspirin.
- Complications of niacin use include impaired glucose tolerance, hepatotoxicity, and hyperuricemia.
- A notable contraindication to niacin use is active peptic ulcer disease.
- The majority of the response to niacin (nicotinic acid) is seen in **two weeks**.

Non-pharmacologic therapy

- Besides pharmacological therapy, the key is to educate the patient on changes in lifestyle and addressing the secondary causes.
- Lifestyle changes include dietary changes such as reduction of carbohydrate intake, avoidance of sugar-sweetened beverages, and processed carbohydrates, regular exercise, and weight loss.

Parhofer KG, Laufs U. The Diagnosis and Treatment of Hypertriglyceridemia. Dtsch Arztebl Int. 2019 Dec 06;116(49):825-832.

Non-pharmacologic therapy

- Weight loss of **5% to 10%** is associated with a reduction of triglyceride levels.
- Similarly, regular aerobic exercise can reduce triglycerides. (at least 150 minutes/week of moderate-intensity activity, 75 minutes/week of vigorous intensity activity, or an equivalent combination of both.
- Many studies have shown that monounsaturated fatty acid-rich Mediterranean-type diet has reduced postprandial lipemia.
- DIET: with a target of <6 percent calories of added sugar and ≤5 to 35 percent calories of total fat. (depend on severity of HTG)
- When triglyceride levels are in excess of 500 mg/dL, restriction of dietary fat is key to avoid a postprandial rise in chylomicrons and thereby reduce the risk of pancreatitis.

Parhofer KG, Laufs U. The Diagnosis and Treatment of Hypertriglyceridemia. Dtsch Arztebl Int. 2019 Dec 06;116(49):825-832.

Non-pharmacologic therapy

- In addition to pharmacotherapy and lifestyle modification, addressing the secondary contributors is important. Alcohol cessation and tighter glycemic control in diabetes are effective strategies to control secondary contributors.
- The primary goal of reduction of triglyceride levels in patients (with triglycerides of more than 500 mg/dL) is to decrease the risk of pancreatitis. When the triglycerides are moderately elevated (200 mg/dL to 500 mg/dL), the goal should be to prevent cardiovascular events and disease.
- Reducing non-HDL cholesterol levels down to 30 mg/dL above the LDL goal helps in cardiovascular risk reduction.

Parhofer KG, Laufs U. The Diagnosis and Treatment of Hypertriglyceridemia. Dtsch Arztebl Int. 2019 Dec 06;116(49):825-832.

The Management of Dyslipidaemia in Pregnancy

Introduction

- There is a physiological increase in plasma concentrations of cholesterol and triglycerides during normal pregnancy, as there is an increased delivery of nutrients to the feto-placental unit. Lipids are required for the rapid growth of the baby and placenta, and a healthy pregnancy.

Introduction

- The plasma lipid concentrations in healthy pregnant women and people do not reflect their usual lipid profile outside of pregnancy, and therefore plasma lipid concentrations are not routinely assessed.
- This temporary increase confers no additional risk to the pregnant individual or baby. In normal pregnancies, blood lipid levels remain elevated for at least one month following the birth of the baby, although triglyceride levels can fall more rapidly in individuals who breastfeed.
- Checking a lipid profile should be delayed for at least 2-3 months following delivery.

Concerns

- However individuals with high serum cholesterol levels before pregnancy, such as those with familial hypercholesterolaemia, may show a more dramatic deterioration of their lipid profile during pregnancy, compared to those with a normal lipid profile. Individuals with very high blood levels of triglycerides before pregnancy may develop severe hypertriglyceridaemia.
- These high levels of plasma triglycerides may be associated with an increased risk of acute pancreatitis. Whilst this is uncommon, it is a very serious complication resulting in severe central abdominal pain and may also be associated with skin manifestations, eruptive xanthoma, a maculopapular rash, that can be widely distributed and intensely itchy.
- In addition, there is an increased risk of adverse outcome in pregnant women and people with hypertriglyceridaemia including pre-eclampsia and fetal growth restriction.

Pregnancy and familial hypercholesterolaemia

- An otherwise healthy woman with familial hypercholesterolaemia (FH) should not be discouraged from becoming pregnant, or breastfeeding their baby.
- However all women with FH who are of childbearing age should be aware of the need for pre-pregnancy counselling prior to embarking on a pregnancy, and what they should do if they have an unplanned pregnancy; 45% pregnancies and 30% of births are unplanned in the UK.
- This information should be revisited at least annually.

Pre-pregnancy counselling

- **An overall risk assessment of coming off standard lipid lowering treatment** whilst attempting to conceive and completing a pregnancy (including the duration of breastfeeding)
- **Medication review and planning**
  - Drugs to stop prior to conception– includes statins and ezetimibe
  - Planned drug regime during pregnancy (including the use of apheresis if indicated) –no lipid lowering therapy (if patient is particularly high risk e.g. secondary prevention and FH consider lipid clinic advice in regards to apheresis and bile acid sequestrants)
  - Additional vitamin supplementation (when bile sequestrants are used) Breastfeeding / chest feeding
- **An assessment of the risk of coronary artery** disease

Pregnancy and lipid-lowering medication

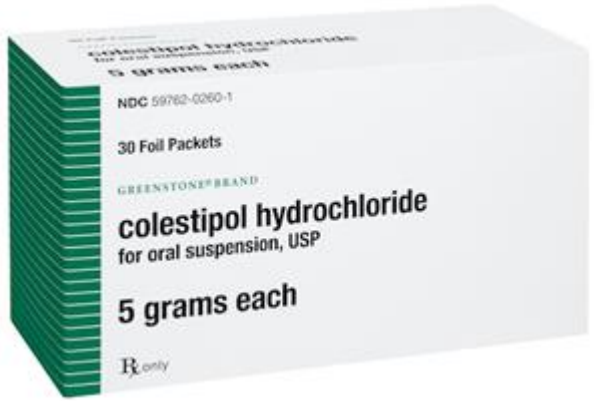
- ✓Women are advised to stop their lipid-lowering medication for at least 1 month, and preferably 3 months before attempting to conceive.

Pregnancy and lipid-lowering medication

- Many cholesterol-lowering medicines, such as statins and ezetimibe can cross the placenta and may potentially harm the unborn baby. Whilst this risk is small, these medications are **contra-indicated during pregnancy** and breastfeeding.
- PCSK-9 inhibitors (alirocumab and evolocumab) are not licenced for use during pregnancy, nor breastfeeding, and again should also be **stopped** before attempting to conceive.
- **Fibrates and omega-3** fatty acids may be considered for patients with hypertriglyceridaemia.

Pregnancy and lipid-lowering medication

- ✓**Bile acid sequestrants** are not absorbed systemically, do not cross the placenta and so are the only cholesterol-lowering medication that can be safely prescribed during pregnancy, and whilst breastfeeding / chest feeding.



Cholestyramine

- **Dosing:** Initial: 4 g 1 to 2 times/day; increase gradually over ≥1-month intervals; maintenance: 8 to 16 g/day divided in 2 doses; maximum: 24 g/day.
- **Administration**
  - Not to be taken in dry form. Suspension should not be sipped or held in mouth for prolonged periods (may cause tooth discoloration or enamel decay).
  - Administration at mealtime is recommended. Twice-daily dosing is recommended but may be administered in 1 to 6 doses daily.
  - In general, administer other oral medications ≥1 hour before or 4 to 6 hours after cholestyramine; consult drug interactions database for additional information.

Colestipol

Dosing

- Granules: Initial: 5 g once or twice daily; increase by **5 g per day** at 1- to 2-month intervals. In patients with preexisting constipation, initiate at 5 g once daily for 5 to 7 days, then increase to 5 g twice daily. Maintenance: 5 to 30 g/day administered once daily or in divided doses.
- Tablets: Initial: 2 g once or twice daily; increase by 2 g once or twice daily at 1- to 2-month intervals. Maintenance: 2 to 16 g/day administered once daily or in divided doses.

Administration

Other drugs should be administered at least 1 hour before or 4 hours after colestipol.

- **Granules:** After mixing and administration of granules, rinse glass with a small amount of liquid and ingest to ensure all medication is taken.
- **Tablets:** Administer tablets 1 at a time, swallowed whole, with plenty of liquid. Do not cut, crush, or chew tablets

Pregnancy and lipid-lowering medication

- ✓Bile acid sequestrants can reduce the absorption of fat-soluble vitamins. **Vitamin D (800- 1000 units once a day)** should be prescribed to prevent deficiency.

- ✓Higher doses may on occasion be needed (secondary care recommendation only on basis of low measured levels).

Breastfeeding / Chest feeding

- For most postnatal women and people, lipid-lowering drug therapy is stopped during breastfeeding/chest feeding. **Treatment with resins can be continued**.
- There are no clinical trials examining the safety of statins in breastfeeding and currently women are advised to avoid statins if breastfeeding.
- Dependent on the lipophilicity of the statin, milk: **serum concentration ratios are reported to be from 0.5-2**. The hydrophilic statins **Rosuvastatin and Pravastatin** may be associated with lower transfer into breast milk.
- Although standard advice is to avoid statins in breastfeeding, **case-by-case advice** for women with FH is recommended.

Pregnancy and hypertriglyceridaemia

- With respect to the treatment of severe hypertriglyceridaemia during pregnancy, whilst **omega-3 fatty acids** can be safely used, there are very limited data for other treatment modalities.
- In very severe hypertriglyceridaemia (Familial Chylomicronaemia Syndrome), **diabetes mellitus** is often a co-morbidity, and improving diabetic control is a critical first step.
- **Fenofibrate and a very low-fat diet combined with omega 3** fatty acids has been suggested for use in **the second trimester.**
- **Apheresis** has also been successfully used in thiscondition although it is nOt easily available locally and may need referral to a specialist centre.

Thank you
Any question?