



Obstetrical Management of Severe Hypertriglyceridemia in Pregnancy: A Case Report

Nigel Madden, MD¹ Nevin Kamal, MD² Jared Friedman, MD² Priya Freaney, MD³
Susan E. Gerber, MD, MPH¹ Emily D. Szmulowicz, MD, MS²

¹Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, Illinois

²Division of Endocrinology, Metabolism and Molecular Medicine, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

³Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois

Address for correspondence Nigel Madden, MD, Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Prentice Women's Hospital, 250 E. Superior Street, 5th Floor, Chicago, IL 60611 (e-mail: nigelmadden@gmail.com).

AJP Rep 2024;14:e244–e249.

Abstract

Background Pregnant people with baseline hypertriglyceridemia are at increased risk of severe hypertriglyceridemia and the associated complications, yet there are no formal recommendations to guide management of these patients during pregnancy.

Case We report a case of a patient with presumed familial hypertriglyceridemia who was taken off triglyceride-lowering medications preconception and developed acute pancreatitis at 23 weeks of gestation. She was managed with a very-low-fat diet, exercise, fenofibrate, omega-3-fatty acids, pravastatin, insulin infusion, and plasmapheresis. She delivered at 33 weeks of gestation after presenting with a placental abruption and subcapsular liver hematoma associated with HELLP (hemolysis, elevated liver enzyme levels, and low platelet) syndrome.

Keywords

- ▶ hypertriglyceridemia
- ▶ pancreatitis
- ▶ fibrate
- ▶ plasmapheresis

Conclusion While rare in pregnancy, severe hypertriglyceridemia is associated with serious maternal risks. Preconception and antepartum obstetric management should incorporate shared decision-making considering both the potential fetal risks of treatment and the objective maternal risks of untreated disease.

Severe hypertriglyceridemia in pregnancy is rare and most cases result from an underlying genetic abnormality in triglyceride (TG) metabolism.^{1,2} In familial hypertriglyceridemia, the physiologic changes of pregnancy exacerbate a preexisting dysregulation in TG homeostasis and increase the risk of hypertriglyceridemia. In early pregnancy, rising progesterone levels result in hyperphagia and increased fat stores. As pregnancy progresses, under the influence of estrogen and human placental lactogen, TG levels increase two- to fourfold because of enhanced hepatic synthesis and increased adipose tissue lipolysis.^{2,3} In the majority of pregnant people, these

elevated TG levels are still below a level that would cause maternal complications.⁴ However, in pregnant people with baseline hypertriglyceridemia, particularly familial hypertriglyceridemia, higher baseline TG levels and impaired metabolism may lead to levels that cross that threshold. Furthermore, discontinuation of TG-lowering medications before or during pregnancy can result in substantially elevated risk of severe hypertriglyceridemia.

Severe hypertriglyceridemia is associated with increased risk of adverse pregnancy outcomes including preeclampsia, fetal growth abnormalities, hyperviscosity syndrome, and

received
August 21, 2024
accepted
August 25, 2024
accepted manuscript online
September 11, 2024

DOI <https://doi.org/10.1055/a-2413-2465>.
ISSN 2157-6998.

© 2024. The Author(s).

This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)

Thieme Medical Publishers, Inc., 333 Seventh Avenue, 18th Floor, New York, NY 10001, USA

maternal pancreatitis.⁵ Hypertriglyceridemia-induced acute pancreatitis (HIAP) is associated with high rates of stillbirth (~23%) and maternal morbidity and mortality (up to 20%).² Despite these risks, most sources recommend discontinuation of TG-lowering medications given the potential for fetal teratogenicity.⁶ We present a case of a patient with suspected familial hypertriglyceridemia who, when untreated and unmonitored in pregnancy, experienced multiple complications including HIAP and offer an outline for obstetrical best practices to guide management of future cases with an emphasis on balancing *both* fetal and maternal risks.

Case

A 38-year-old nulliparous female with a pregnancy conceived by in vitro fertilization presented at 23 1/7 weeks of gestation with acute abdominal pain, nausea, and vomiting. She had a history of suspected familial hypertriglyceridemia, well controlled outside of pregnancy on a low-fat diet, fish oil, and fenofibrate. Both the fish oil and fibrate were discontinued prior to conception. Her pregnancy was notable for a lower extremity deep vein thrombosis (DVT) at 8 weeks that was treated with enoxaparin. Upon presentation she had normal vital signs. Laboratory studies demonstrated a leukocytosis ($21 \times 10^3/uL$) and elevated lipase (154 u/L). TG levels were severely elevated at 1,530 mg/dL. Computed tomography (CT) revealed acute interstitial pancreatitis and she was transferred to the medical intensive care unit (ICU).

►Fig. 1 demonstrates her 3-week hospital course. Initial management with intravenous insulin infusion resulted in a decline in TG levels to 450 mg/dL over 2 days. The insulin infusion was discontinued and she started a very-low-fat diet. On hospital day 3, TG levels rebounded to 905 mg/dL, necessitating resumption of the insulin infusion. Her TG levels were highly sensitive to insulin, requiring frequent

reinitiation of the infusion as oral management strategies were trialed. Icosapent ethyl 2 g twice daily and fenofibrate 145 mg daily were introduced on day 3 and day 4, respectively. On day 12, pravastatin was added. Despite these medications, her TG levels continued to rebound when off insulin and she underwent a single round of plasmapheresis on hospital day 14. The insulin infusion was discontinued, and her TG levels remained < 1,000 mg/dL. On hospital day 21, she was discharged. Outpatient management included three times weekly TG monitoring and treatment with daily aerobic exercise, a very-low-fat diet, icosapent ethyl, fenofibrate, and pravastatin. TG levels remained < 1,000 mg/dL.

At 33 5/7 weeks of gestation, she presented with severe right upper quadrant pain. Vital signs were normal. Labs showed stable TG levels (858 mg/dL), normal lipase, elevated aspartate transaminase (AST) (86 u/L), alanine transaminase (ALT) (62 u/L), and lactate dehydrogenase (LDH). A prolonged fetal heart rate deceleration was noted and she underwent an emergent cesarean delivery. At delivery, the amniotic fluid was bloody consistent with presumed placental abruption. Labs demonstrated rising transaminases (AST 2,630 u/L, ALT 2,994 u/L), downtrending platelets ($135 \times 10^3/uL$), and rising LDH (1,627 u/L) concerning for HELLP (hemolysis, elevated liver enzyme levels, and low platelet) syndrome. CT imaging demonstrated an 18-cm subcapsular liver hematoma without active bleeding and the patient was transferred to the ICU. She was managed conservatively, receiving 3 units of packed red blood cells for a hemoglobin of 5.5 g/dL, and was discharged on postpartum day 9 on fenofibrate and icosapent ethyl. TG levels at 2 months postpartum were 102 mg/dL.

Discussion

Pregnant individuals with familial hypertriglyceridemia are at high risk of complications from hypertriglyceridemia due

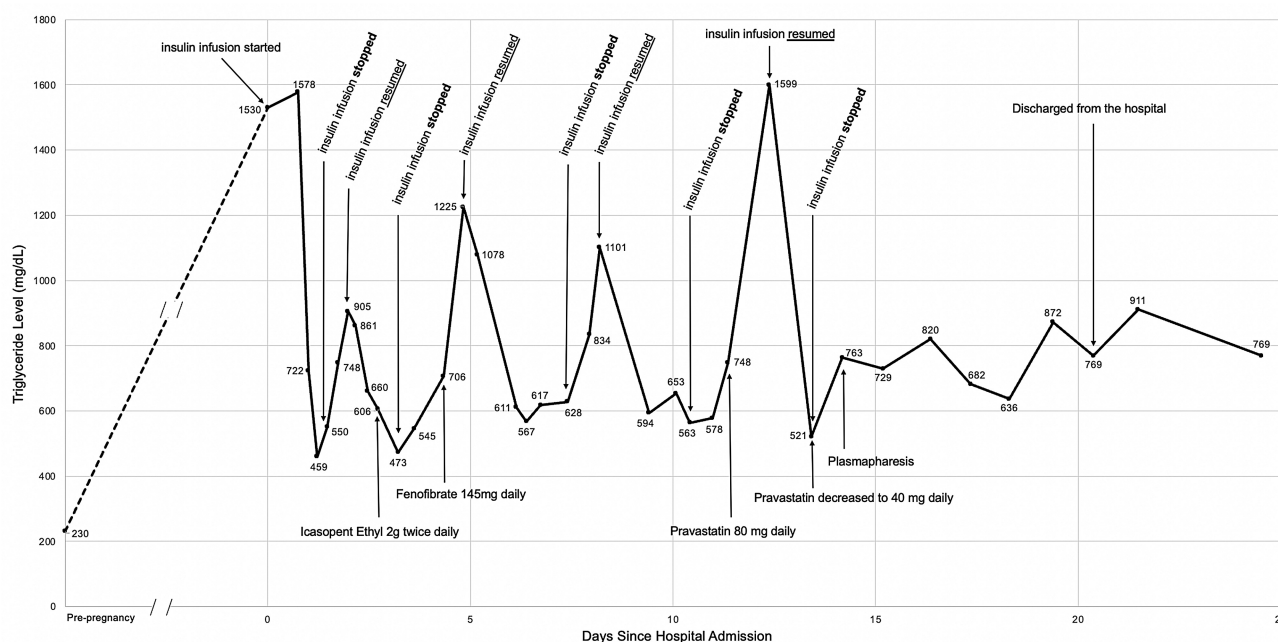


Fig. 1 Patient 21-day hospital course during admission for acute pancreatitis.

to the inability to appropriately regulate the normal physiologic changes in lipid metabolism in pregnancy.^{1,2} To date, there are no formal recommendations to guide management of hypertriglyceridemia during pregnancy, particularly regarding the use of TG-lowering medications, and literature emphasizes the unproven *potential* for fetal risk without acknowledging the well-documented maternal risk of untreated disease.⁶ In this case, TG-lowering medications were discontinued preconception, the patient did not have follow-up monitoring of her TG levels, and she ultimately experienced serious complications related to her hypertriglyceridemia. Her course highlights the need to critically evaluate the accepted norms for management and the importance of

jointly delineating a plan for management, considering *both* fetal and maternal risks.

There are serious maternal risks of untreated hypertriglyceridemia and the patient presented here developed several including a DVT and HIAP which required a prolonged ICU admission. She also experienced placental abruption and subcapsular liver hematoma thought to be due to HELLP syndrome, resulting in premature delivery. Studies suggest that hypertriglyceridemia increases the risk of pre-eclampsia by exacerbating endothelial dysfunction and placental ischemia.⁷ It is possible that this mechanism is responsible for the association between hypertriglyceridemia and HELLP syndrome seen in this case.

Table 1 Treatment options for hypertriglyceridemia in pregnancy

Treatment	Formulation/Dosing	Mechanism of action	Effect on TG levels	Effect on pregnancy
Fat-restricted diet ^{2,5,12} Moderate-intensity aerobic exercise ¹⁵	< 20% of total calories (can consider lower) 150 min/week (e.g., 30 min 5 days/week) at least	Reduce chylomicron formation and TG synthesis	Variable	Maternal weight loss Concern for fetal essential fatty acid deficiency (supplement with omega-3-fatty acids ± MCT)
Omega-3-fatty acids ^{2,5,12} Contain eicosapentaenoic acid (EPA) ± docosahexaenoic acid (DHA)	Vascepa (EPA) or Lovaza (EPA + DHA) Dosing: 2–4 g/d	Decrease hepatic TG synthesis Increase fatty acid oxidation Stimulate LPL activity	Decrease TG levels by 20–50%	No studies suggesting increased risk of use in pregnancy Supplementation may be necessary to prevent fetal fatty acid deficiency which can lead to impaired brain and visual development Theoretical increased bleeding risk though RCTs in pregnancy and outside of pregnancy have not demonstrated this ^{16–18}
Fibrates ^{2,5,12}	Fenofibrate dosing: 145 mg daily Gemfibrozil dosing: 600 mg twice per day (before breakfast/dinner)	Upregulation of LPL transcription Decrease hepatic TG synthesis by induction of hepatic free fatty acid oxidation Stimulate reverse cholesterol transport	Decreases TG levels by 50%	Several case reports and small cohort studies have not shown increased risk of teratogenicity or adverse pregnancy outcomes
Statins ^{5,13,14}	Pravastatin (lipophilic, theoretically lower risk of transplacental transfer) Dosing: 40–80 mg/d	Primarily reduce LDL and vLDL Also has a modest TG-lowering effect	Decrease TG levels by 10–30%	Meta-analysis demonstrated no increased risk of teratogenicity, possible increased risk of miscarriage ¹⁴ FDA has recommended removing the category X label
Niacin ^{2,8,12} (generally, not recommended)	Dosing: 1,500–3000 mg/d to have TG-lowering effect (maximum recommended dose in pregnancy 30–35 mg/d)	Reduce hepatic synthesis Reduce hepatic free fatty acid breakdown	Decrease TG levels by 15–20%	Used in rare case reports Limited data on the impact of the high dose required for TG-lowering effect
Insulin ^{2,12}	Regular insulin Insulin drip protocol per hospital guidelines Simultaneous D5 0.45% NS infusion usually needed to maintain euglycemia with hourly blood glucose monitoring and adjustment of D5 infusion as indicated	Rapid and potent activator of LPL	Rapidly lowers TG levels	Risk of hypoglycemia May require ICU-level care
Plasmapheresis ^{2,5,9,12}	Protocol per hospital guidelines	Rapidly remove TG-rich lipoprotein Remove inflammatory mediators and cytokine levels in acute pancreatitis	Lowers TG levels by 50–80% (transient)	Requires central access (risk of infection, thrombosis) Transient effect requiring multiple sessions with high cost Similar rates of adverse events as compared to nonpregnant population

Abbreviations: D5, dextrose 5%; FDA, Federal Drug Administration; ICU, intensive care unit; LDL, low-density lipoprotein; LPL, lipoprotein lipase; MCT, medium chain triglycerides; NS, normal saline; RCT, randomized controlled trial; TG, triglyceride; vLDL, very low-density lipoprotein.

► **Table 1** lists treatment options for hypertriglyceridemia. As outlined, these options have variable evidence of risk in pregnancy. Omega-3-fatty acids are a first-line treatment and can lower TG by up to 50%.^{2,5} There have been no studies to suggest increased risk with supplementation in pregnancy. In fact, all prenatal vitamins contain omega-3-fatty acids and supplementation with essential fatty acids is *recommended* in the setting of a very-low-fat diet as fetal deficiency of these fatty acids can lead to impaired brain development.^{2,8} Fibrates are another first-line treatment for hypertriglyceridemia outside of pregnancy and can lower TG levels by up to 50%.^{2,5} Given limited data on safety, previous authors recommend discontinuation of fibrates prior to conception with resumption only after the first trimester. Although there have been no randomized controlled trials, there have been case series with fibrate use later in pregnancy and a nationwide cohort study in South Korea of fibrate use in the first trimester that have shown no increased risk of congenital anomalies or adverse outcomes.^{1,8–12} Statins have a more modest TG-lowering effect (10–30%).⁵ Statins were previously labeled category X by the Federal Drug Administration (FDA), yet more recent evidence has demonstrated safety, prompting the FDA to recommend

removing the category X label.^{13,14} However, given their limited TG-lowering effect, statins are typically not first-line therapy. Given the lack of data to suggest increased risk of these medications in pregnancy, it is reasonable to take an individualized, shared decision-making approach that openly discusses the limitations of existing literature and the implications for both the fetus and mother, rather than broadly recommending discontinuation.

Additionally, there is scarce literature offering comprehensive obstetrical recommendations for management of patients with baseline hypertriglyceridemia throughout pregnancy. In ► **Table 2** we provide a framework for management. When possible, management should begin *preconception* with lifestyle interventions including weight loss, diet, and regular exercise and a goal to reach TG levels of < 150 mg/dL prior to pregnancy. Upon initial presentation to care, we recommend reviewing the risks and benefits of continuing TG-lowering medications during pregnancy. If discontinuing TG-lowering therapy, a clear plan for monitoring off therapy should be delineated. TG levels should be checked at the first visit and monitored serially.

► **Fig. 2** outlines a TG monitoring plan with recommended interventions depending on the TG level. A fat-restricted diet

Table 2 Framework for the management of hypertriglyceridemia in pregnancy

Time period	Counseling	Maternal management	Fetal/Obstetric management
Preconception	<ul style="list-style-type: none"> • Discuss importance of weight loss, diet, regular exercise • Shared decision-making on the risks and benefits of continuing TG-lowering medications 	<ul style="list-style-type: none"> • Check fasting lipid levels • Optimize glycemic management if indicated • Consider referral to a preventative cardiologist to help implement key lifestyle changes prior to pregnancy 	
Throughout pregnancy	<ul style="list-style-type: none"> • Shared decision-making on the risks and benefits of continuing TG-lowering medications 	<ul style="list-style-type: none"> • Assess for symptoms of pancreatitis every visit • Monitor weight gain closely; clinical weight loss should prompt reassessment of dietary restrictions/recommendations • If TG levels are rising despite management or > 1,000 mg/dL at any point, consider admission for monitored diet and multidisciplinary planning 	
First trimester	<ul style="list-style-type: none"> • Discuss risks of severe hypertriglyceridemia in pregnancy • Discuss plan for monitoring TG levels and when to consider medical management (if choosing not to continue in first trimester) • Discuss signs/symptoms of pancreatitis and when to present to the hospital 	<ul style="list-style-type: none"> • Initiate multidisciplinary team management with MFM or OB, endocrinology, and nutrition • Baseline fasting lipid levels and A1c • Repeat TG levels at least monthly (see ► Fig. 2) • If TG levels > 250 mg/dL, discuss low-fat diet and omega-3-fatty acid supplementation • Recommend moderate-intensity aerobic exercise of at least 150 min/week (ACOG guidelines) • Consider aspirin for preeclampsia prevention 	
Second trimester		<ul style="list-style-type: none"> • Continue TG monitoring • Consider adding a fibrate depending on TG levels • Screen for gestational diabetes at 24–28 weeks of gestation 	<ul style="list-style-type: none"> • Detailed anatomic survey if TG-lowering medications are continued in first trimester
Third trimester		<ul style="list-style-type: none"> • TG monitoring every 2 weeks in the 3rd trimester given expected rise in TG levels • Delivery before 39 weeks is not indicated unless severe hypertriglyceridemia refractory to treatment in the third trimester • Route of delivery per routine obstetric considerations 	<ul style="list-style-type: none"> • Serial fetal growth ultrasounds • Weekly nonstress tests starting at 32 weeks' gestation if TG levels are elevated
Postpartum	<ul style="list-style-type: none"> • Shared decision-making on the risks and benefits of continuing TG-lowering medications with breastfeeding (limited data) 	<ul style="list-style-type: none"> • Ensure long-term primary care and cardiology follow-up plan in place 	<ul style="list-style-type: none"> • Pediatric follow-up and genetic testing as indicated

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; MFM, maternal fetal medicine; OB, obstetrician; TG, triglyceride.

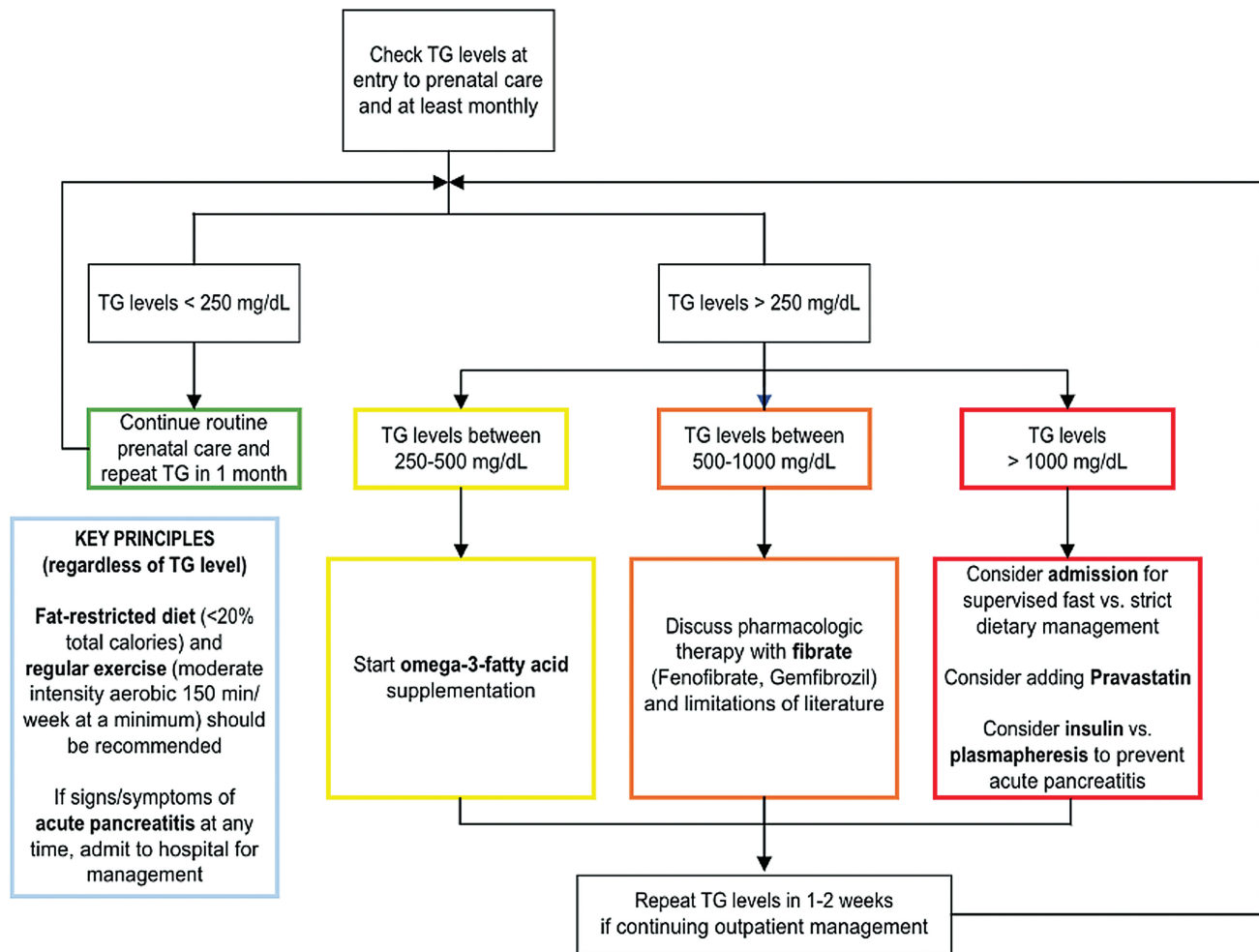


Fig. 2 Triglyceride level monitoring and management recommendations. TG, triglyceride.

and regular exercise should be recommended for all patients. If the TG levels rise above 250 mg/dL, omega-3-fatty acid supplementation should be initiated. If the TG levels surpass 500 mg/dL, pharmacologic treatment with fibrates should be considered. If the TG levels continue to rise despite pharmacologic intervention or if they surpass 1,000 mg/dL, the patient should be admitted for a supervised fast or strict dietary monitoring. If the levels remain poorly controlled, a multidisciplinary team should consider more expeditious lowering of TG levels with intravenous insulin or plasmapheresis. If the patient develops signs or symptoms of pancreatitis at any time, urgent evaluation with likely admission to the ICU is warranted.

Fetal monitoring is recommended with a detailed anatomic survey if TG-lowering medications are continued in the first trimester and serial growth ultrasounds in the third trimester. If TG levels are elevated, we recommend antenatal testing with weekly nonstress tests starting at 32 weeks' gestation. Delivery timing and route should be determined by routine obstetric practice.

Hypertriglyceridemia in pregnancy is a high-risk condition that requires close, multidisciplinary monitoring throughout pregnancy. Although limited, data on TG-lowering medications in pregnancy are growing, and it is important that management decisions are made using a shared

decision-making approach that considers both the potential fetal risks of treatment with the objective maternal risks of untreated disease.

Conflict of Interest

None declared.

References

- 1 Cao S, Dao N, Roloff K, Valenzuela GJ. Pregnancies complicated by familial hypertriglyceridemia: a case report. *AJP Rep* 2018;8(04): e362–e364
- 2 Wong B, Ooi TC, Keely E. Severe gestational hypertriglyceridemia: a practical approach for clinicians. *Obstet Med* 2015;8(04): 158–167
- 3 Gupta M, Liti B, Barrett C, Thompson PD, Fernandez AB. Prevention and management of hypertriglyceridemia-induced acute pancreatitis during pregnancy: a systematic review. *Am J Med* 2022;135(06):709–714
- 4 Piechota W, Staszewski A. Reference ranges of lipids and apolipoproteins in pregnancy. *Eur J Obstet Gynecol Reprod Biol* 1992; 45(01):27–35
- 5 Bashir M, Navti OB, Ahmed B, Konje JC. Hyperlipidaemia and severe hypertriglyceridaemia in pregnancy. *Obstet Gynaecol* 2023;25:196–209
- 6 Jacobson TA, Maki KC, Orringer CE, et al; NLA Expert Panel. National lipid association recommendations for patient-centered

- management of dyslipidemia: part 2. *J Clin Lipidol* 2015;9(6, Suppl):S1–122.e1
- 7 Poornima IG, Indaram M, Ross JD, Agarwala A, Wild RA. Hyperlipidemia and risk for preeclampsia. *J Clin Lipidol* 2022;16(03):253–260
 - 8 Goldberg AS, Hegele RA. Severe hypertriglyceridemia in pregnancy. *J Clin Endocrinol Metab* 2012;97(08):2589–2596
 - 9 Choi J, Kim H, Jun J, Ryu J, Lee HY. Recurrent pancreatitis in a pregnant woman with severe hypertriglyceridemia successfully managed by multiple plasmapheresis. *J Atheroscler Thromb* 2022;29(07):1108–1116
 - 10 Gupta N, Ahmed S, Shaffer L, Cavens P, Blankstein J. Severe hypertriglyceridemia induced pancreatitis in pregnancy. *Case Rep Obstet Gynecol* 2014;2014:485493
 - 11 Kay HY, Jang HY, Kim IW, Oh JM. Fibrates and risk of congenital malformations: a nationwide cohort study in South Korea. *Arch Gynecol Obstet* 2024;310(04):1967–1973
 - 12 Nguyen NT, Nath PV, Mai VQ, Shakir MKM, Hoang TD. Treatment of severe hypertriglyceridemia during pregnancy with high doses of omega-3 fatty acid and plasmapheresis. *AACE Clin Case Rep* 2021;7(03):211–215
 - 13 Mauricio R, Khera A. Statin use in pregnancy: is it time for a paradigm shift? *Circulation* 2022;145(07):496–498
 - 14 Karadas B, Uysal N, Erol H, et al. Pregnancy outcomes following maternal exposure to statins: a systematic review and meta-analysis. *Br J Clin Pharmacol* 2022;88(09):3962–3976
 - 15 ACOG Committee Opinion No. 804: physical activity and exercise during pregnancy and the postpartum period: correction. *Obstet Gynecol* 2021;138(04):683
 - 16 Harris WS. Expert opinion: omega-3 fatty acids and bleeding—cause for concern? *Am J Cardiol* 2007;99(6A):44C–46C
 - 17 Middleton P, Gomersall JC, Gould JF, Shepherd E, Olsen SF, Makrides M. Omega-3 fatty acid addition during pregnancy. *Cochrane Database Syst Rev* 2018;11(11):CD003402
 - 18 Olsen SF, Sørensen JD, Secher NJ, et al. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. *Lancet* 1992;339(8800):1003–1007