REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Prevention and Management of Hypertriglyceridemia-Induced Acute Pancreatitis During Pregnancy: A Systematic Review

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ABSTRACT

Severe gestational hypertriglyceridemia can lead to acute pancreatitis, with maternal mortality rate of approximately 20%. The recent National Lipid Association part 2 expert panel recommendations provide guidance on monitoring pregnant women at high risk for hyperlipidemia. We suggest that high-risk women have triglyceride levels checked once every trimester. Fasting triglycerides >250 mg/dL should prompt monthly triglyceride levels, screening for gestational diabetes, and implementing a strict low-carbohydrate, low-fat diet, exercise. Fasting triglycerides >500 mg/dL, despite a strict dietary and lifestyle modifications, should prompt treatment with omega-3-fatty acids and continue a fat-restricted diet (<20 g total fat/d or <15% total calories) under the guidance of a registered dietician. The use of fibrates should be considered as a second-line therapy due to their unclear risk versus benefit and potential teratogenic effects. Plasmapheresis should be considered early in asymptomatic pregnant women with fasting triglyceride levels >1000 mg/dL or in pregnant women with clinical signs and symptoms of pancreatitis and triglyceride levels >500 mg/dL despite maximal lifestyle changes and pharmacologic therapy.

Published by Elsevier Inc. • The American Journal of Medicine (2022) 135:709−714

KEYWORDS: Cardio-obstetrics; Hypertriglyceridemia; Pancreatitis; Pregnancy

INTRODUCTION

Pancreatitis during pregnancy is rare with a prevalence estimated at 1 in 1000 to 10,000 pregnancies.[1,2] Pancreatitis during pregnancy is more common in multiparous women, especially in the third trimester or early postpartum period.[1] It is also more frequent in women with a history of gallstones, high alcohol consumption, high-fat and high-refined/simple carbohydrate diets, and a family history of hypertriglyceridemia.[1,3]

Plasma triglyceride (TG) levels can increase 2- to 4-fold during the third trimester of pregnancy and can produce very high TG levels in some women, driven by an increased TG-rich lipoprotein production and decreased lipoprotein lipase activity.[4] Hypertriglyceridemia-induced pancreatitis in pregnancy is associated with a maternal mortality rate as high as 20%.[5] Hypertriglyceridemia in pregnancy can be accompanied by preeclampsia and hyperviscosity syndrome characterized by neurological symptoms, bleeding, and heart failure, but the most dangerous complication is life-threatening pancreatitis.[6,7] TG-lowering treatment options during pregnancy are limited by the potential teratogenicity of current pharmacologic treatments. We review the literature and provide recommendations for the management of markedly elevated TG levels during pregnancy and the prevention and treatment of TG-induced pancreatitis.

METHODS

We performed a systematic literature search on PubMed using the MeSH terms “pregnancy,” “hypertriglyceridemia,” “treatment,” and “pancreatitis” alone and in combinations for articles published in English from 1980 through 2021.

Funding: All funding and support for this work came from within the Division of Cardiology at Hartford Hospital.

Conflicts of Interest: None.

Authorship: All authors had access to the data and a role in writing this manuscript.

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0002-9343/Published by Elsevier Inc.
https://doi.org/10.1016/j.amjmed.2021.12.006

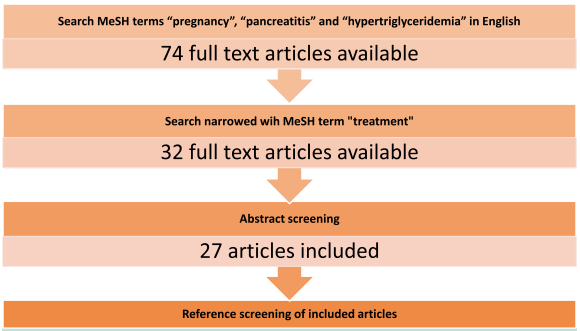

Figure 1 Summary of results for systematic literature search.

Only publications in English language were included. We identified abstracts and reviewed relevant articles in detail. Older references from these articles were also reviewed. There was scant data on the topic of hypertriglyceridemia-induced pancreatitis and no case-control trials; thus, articles including a small number of patients such as case studies and case series were included. No review articles were included. The process is included in Figure 1.

CLINICAL SIGNIFICANCE

- At the first visit and at the beginning of the third trimester of pregnancy triglycerides are assessed.
- Triglycerides >225 mg/dL should prompt monthly surveillance, exercise, optimized diet, and alcohol avoidance.
- If triglycerides are >500 mg/dL despite optimal diet, omega-3 fatty acids should be initiated.
- Use plasmapheresis in refractory cases with triglyceride levels >1000 mg/dL and in hypertriglyceridemia-induced pancreatitis and stop when triglyceride levels <400 mg/dL without signs or symptoms of pancreatitis.

RESULTS

The initial search for "pregnancy," "hypertriglyceridemia," and "pancreatitis" yielded 74 articles. Adding "treatment" to this search resulted in 32 total articles in peer-reviewed journals. Of these 32, only 27 were available as full-text English-language articles that discussed cases (Figure 1).

DISCUSSION

Triglyceride Metabolism During Pregnancy

An analysis of lipid levels during 74,356 pregnancies demonstrated that TG levels decrease during the first trimester with a nadir between the second and third month. This is followed by a gradual increase during subsequent trimesters to a peak before delivery.[8-10] Elevation of TG levels of 2- to 4-fold by the third trimester of pregnancy is expected and well tolerated. TG levels usually remain below 250 mg/dL and rarely exceed 332 mg/dL (the 95th percentile value for TG levels during pregnancy).[8,10]

Under normal circumstance, these changes in lipids are beneficial to fetal development because lipids are required to develop cell membranes and organogenesis. The increase in serum estrogen and human placental lactogen (HPL) levels during late gestation are responsible for this steady rise in the major lipoproteins and TG levels through term. Increased estrogen levels (especially in the second and third trimester) appear to increase TG levels by inducing hepatic synthesis of very-low-density lipoprotein (VLDL) in conjunction with impaired TG lipolysis due to estrogen-mediated inhibition of lipoprotein lipase (LPL).[9] human placental lactogen also results in inhibition of LPL by increasing insulin resistance and further increases TG levels by stimulating lipolysis in adipocytes. Notably, progesterone increases adipogenesis in the first trimester, resulting in an anabolic state.[4]

Gestational hypertriglyceridemia, defined as TG levels above the 95th percentile of age-adjusted values in females who are not pregnant, is often seen in patients with genetic mutations in key enzymes involved in the TG metabolic process. Mutations in the genes encoding LPL and apolipoprotein (Apo) E and ApoC2 can cause hypertriglyceridemia. Patients with familial chylomicronemia syndrome are at particularly increased risk of having exceedingly high TG levels. Nongenetic causes may also exacerbate the condition, such as diabetes, excessive alcohol intake, metabolic syndrome, HIV with lipodystrophy, and renal disease. Certain medications, such as atypical antipsychotic agents, oral estrogen therapy, noncardioselective beta-blockers, thiazide diuretics, retinoic acid derivatives, antirejection medications, bile acid-binding resins, and corticosteroids have also been shown to increase TG levels.[11]

TG levels above 250 mg/dL during pregnancy are associated with a higher incidence of gestational diabetes, preeclampsia, hyperviscosity syndrome, and acute pancreatitis.[12-14]

Pancreatitis and Pregnancy

Pregnancy-related pancreatitis was first described in 1918 and currently has a prevalence of 19%, 26%, 53%, and 2% during the first, second, and third trimesters and postpartum, respectively.[15,16] Pancreatitis during pregnancy is not always caused by hypertriglyceridemia. A retrospective review of a Beijing Hospital records identified only 36 cases of acute pancreatitis among 34,292 pregnant women between January 1, 1991 and March 31, 2014.[17] In a retrospective study in Beijing, only 14 out of 34,292 pregnant patients (39%) had hypertriglyceridemia listed as the cause of the acute pancreatitis between 1991 and 2014. Furthermore, the diagnosis of severe acute pancreatitis was more frequent among women with TG level >204 mg/dL (11 out

of 14 [79%]) than among those with TG levels <204 mg/dL (6 out of 22 [27%]; $P = .006$).[17] Patients with hypertriglyceridemia with pancreatitis more frequently experienced pregnancy complications (11 [79%] vs 4 [18%]; $P < .001$). Six (17%) patients with severe acute pancreatitis experienced fetal loss.[17]

The mechanism mediating hypertriglyceridemia-induced acute pancreatitis, in general and during pregnancy, is not fully understood. Free fatty acids derived from TG hydrolysis by pancreatic lipase may injure pancreatic cells. Alternatively, large chylomicrons may block pancreatic capillaries producing ischemia.[18]

Diagnosis and Management of Hypertriglyceridemia in Pregnancy

Diagnosis. An initial medical assessment for pregnant women should include evaluation of risk factors associated with hypertriglyceridemia as well as any family history that may point to a possible familial dyslipidemia syndrome. Prompt diagnosis and treatment of gestational diabetes and strict glycemic control in pregnant women with preexisting diabetes can prevent the development of severe hypertriglyceridemia. The American College of Obstetricians and Gynecologists (ACOG) suggest lipid assessment of female patients prior to pregnancy at their annual doctor's visit.[19] These guidelines also suggest that patients with a body mass index (BMI) ≥30 kg/m^2, personal history of gestational diabetes, or known impaired glucose metabolism should be screened for gestational diabetes at the first prenatal visit.[8] Providers should pay special attention to medications that may affect lipid profiles including antipsychotics, beta-blockers, bile acid sequestrants, contraceptive pills, hormone therapy, thiazides, steroids, retinoids, and protease inhibitors.[1] Social history should include questions about alcohol use and quantity and diet type. Laboratory testing should include thyroid function and liver function tests, fasting glucose, and glycosylated hemoglobin (HbA1c).[19] Women who have elevated TG levels, pregnancy-induced-hypertension, preeclampsia, gestational diabetes, or albuminuria during their pregnancy should be evaluated for residual cardiometabolic risk postpartum.[20]

Lifestyle Changes. The most recent recommendation of monitoring and treating hypertriglyceridemia in pregnancy come from the National Lipid Association consensus paper published in December 2015.[8,21] Based on our review, we suggest that all pregnant patients should have their TG levels measured at their first prenatal visit (baseline) and at the beginning of the third trimester because this is the time during pregnancy when TG levels reach the highest levels under the influence of elevated estrogen. High-risk pregnant women should have TG levels measured at the beginning of the first and second trimester as well as monthly checks during their third trimester. Furthermore, we recommend that in cases of TG levels >250 mg/dL at any point during the pregnancy, the patient should undergo close clinical monitoring with monthly TG measurements from that point on and should be advised of dietary changes focused on low-fat, low-glycemic-index foods.[8,10] Patients can be initiated on <20% fat-derived caloric count in the day, avoidance of simple carbohydrates, and supplementation with essential fatty acids (omega-3 fatty esters 3 g/d and medium chain triglycerides 15 g/d) to prevent deficiency.[12,22] A case report described a 26-year-old female with LPL deficiency who was successfully managed through 2 pregnancies by reducing fat caloric intake from 20% prepregnancy to 10.7% at week 25 of gestation with administration of 12 g/d of nonprescription omega-3 fatty acids. Both pregnancies were uncomplicated and the babies were delivered via cesarean section at 38 and 36 weeks, respectively. [7] Both infants have also demonstrated subsequent normal developmental milestones.

Pharmacological Therapy. Consensus suggests that pharmacotherapy becomes necessary if TG levels exceed 500 mg/dL despite optimal diet and lifestyle modifications, as outlined previously. Typically, TG-lowering drugs are discontinued at least 3 months prior to conception in women with prepregnancy hypertriglyceridemia.[8,23] The only lipid-lowering medications currently acceptable to use during pregnancy are the bile acid-binding resins cholestyramine and colesevelam.[24] Although these medications do not pass into the systemic circulation and are safe to the fetus, they raise TG levels and are thus contraindicated in patients who have hypertriglyceridemia. According to safety labels by the US Food and Drug Administration (FDA) as highlighted in the Table, the prescription of omega-3 polyunsaturated fatty acids should be reserved for

Table Categories Previously Established by the FDA to Indicate the Potential of a Drug to Cause Birth Defect if Used During Pregnancy

Triglyceride-Lowering Medication	Pregnancy Category
Statins	X - Contraindicated in pregnancy
Fibrates	C - Risk in pregnancy cannot be ruled out
Nicotinic acid	C - Risk in pregnancy cannot be ruled out
Colesevelam	B - Risk in pregnancy cannot be ruled out
Icosapent Ethyl (Vascepa)	C- Risk in pregnancy cannot be ruled out
Omega-3-acid Ethyl Esters	C - Risk in pregnancy cannot be ruled out
Ezetimibe	C - Risk in pregnancy cannot be ruled out
Cholestyramine	C - Risk in pregnancy cannot be ruled out

FDA = Food and Drug Administration

Pregnancy category listed for each drug with the new FDA category labeling next to the former labeling guidelines.

patients in whom the benefit from drug therapy justifies the potential risk to fetus, after a thorough discussion of these risks and benefits with the patient.[25] Fibric-acid derivatives and nicotinic acid demonstrate skeletal and developmental teratogenic effects in animal models, explaining the FDA designation of category C (unclear teratogenicity).[24] There are, however, 2 case reports that described the use of niacin, gemfibrozil, and fenofibrate after the first trimester with no obvious teratogenic or toxic effects to the fetus or the mother. One case report described a 39-year-old pregnant woman with a history of gestational hypertriglyceridemia and acute pancreatitis treated with niacin and fenofibrate starting at 12 weeks of gestation. She did well until 29 weeks of gestation when she presented with acute pancreatitis and TG levels of 1735 mg/dL. These increased to 3810 mg/dL, necessitating the baby's successful delivery by cesarean section.[4] Another report described a 26-year-old pregnant woman with LPL deficiency and hypertriglyceridemia treated with gemfibrozil, omega-3 fatty acids, and a strict low-fat diet of during 2 out of her 3 pregnancies. This patient had successful pregnancies without hypertriglyceridemia-related complications.[7] Fibric-acid derivatives could, therefore, be considered after the first trimester if TG levels remain >500 mg/dL despite the use of omega-3 fatty acids and dietary restrictions, and other treatments options, such as plasmapheresis, are not available.

Severe cases of gestational hypertriglyceridemia may require temporary inpatient treatment with insulin infusion, which acts by stimulating LPL activity.[5] The use of insulin drip may be more useful in the setting of hyperglycemia and diabetes-induced hypertriglyceridemia. In cases of gestational hypertriglyceridemia that does not respond to conventional dietary and pharmacologic treatments (ie, fasting TG levels remain >1000mg/dL), plasmapheresis can rapidly lower TG levels.[26-28] Review of literature indicates that early initiation of plasmapheresis treatment in high-risk patients or patients with familial hypertriglyceridemia may prevent hypertriglyceridemia-related complications during pregnancy. We suggest considering plasmapheresis in any patient with clinical signs and symptoms of acute pancreatitis and fasting TG levels >700 mg/dL when no other cause for the acute pancreatitis can be discerned. The apheresis treatments should be continued daily until fasting TG levels fall below 400 mg/dL or until the resolution of signs or symptoms of pancreatitis. In pregnant patients without a diagnosis of gestational hypertriglyceridemia-induced acute pancreatitis, plasmapheresis should be strongly considered when TG levels increase above 1000 mg/dL despite dietary restrictions and medical treatment, given the high mortality risk to mother and fetus should acute pancreatitis develop.

Although the TG reduction derived from statin use is modest, statins are designated category X by the FDA. The teratogenic effects of the class are best studied in lipophilic members of the class (ie, lovastatin, cerivastatin, and fluvastatin).[24] A summary of 249 pregnancies from 1990 to 2009 in which the patient reported statin exposure during the pregnancy found that the rate of major birth defect and miscarriages was slightly, but not statistically significantly, higher in the statin-exposure group.[29] Premature births were more common (P = .019) with statins, but the median gestational age and birth weight did not differ between the groups.[29] Another literature review evaluated data on the possible teratogenic effects of statins during pregnancy and discussed 3 case reports.[30] The use of pravastatin, fluvastatin, and atorvastatin until the 24th, 9th, and 8th week of gestation, respectively, was not associated with birth defects or developmental delays.[30] This systematic review included case reports, case series, and registry-based studies, and prospective observational cohorts concluded that human teratogenic risk of statin use has not been conclusively established nor excluded.[30] Figure 2 provides a visual summary of our recommendations on monitoring and treatment.

Diagnosis and Treatment of Severe Triglyceride-Induced Pancreatitis of Pregnancy

There are no specific standards for the diagnosis of acute pancreatitis in pregnancy, although standards for diagnosis and prognosis have been well established in female patients who are not pregnant. Generally, an elevation of serum amylase and lipase 3 times the normal limit has a good positive predictive value for the diagnosis of acute pancreatitis in pregnancy. Imaging using abdominal ultrasound is a safe option in pregnancy because it does not involve radiation to the fetus and has higher sensitivity for detecting gallstones when compared with computed tomography (CT). Magnetic resonance imaging (MRI) is also an option for further assessment of acute pancreatitis and its complications in pregnant women and is safe for the fetus even if gadolinium is used.[1]

The American Society of Apheresis (ASFA) Sixth Edition of Guidelines on the Use of Therapeutic Apheresis in Clinical Practice[31] states that the optimum role of apheresis therapy in the treatment of pancreatitis secondary to hypertriglyceridemia is not established and that decisions on its use should be individualized. They consider recommending its use as weak with only low-quality or very-low-quality evidence from observational studies or case series.[31] Immunoadsorption removes pathogenic substances more selectively, thereby avoiding the substitution of fresh-frozen plasma.[5] A comparison of the effectiveness of 3 different modalities of extracorporeal lipid removal low-density lipoprotein immunoadsorption, plasma exchange, and combined treatment of plasma exchange followed by immunoadsorption found that plasma exchange provided a higher efficacy of lipid-lowering but was associated with an increased bleeding rate. Fresh-frozen plasma administration mitigated the bleeding risk, but this is known to increase viral infection risk.[5] As the gestational age progresses in cases of severe familial hypertriglyceridemia, the patient's plasmapheresis requirements increase, and the response to every treatment decreases.[27]

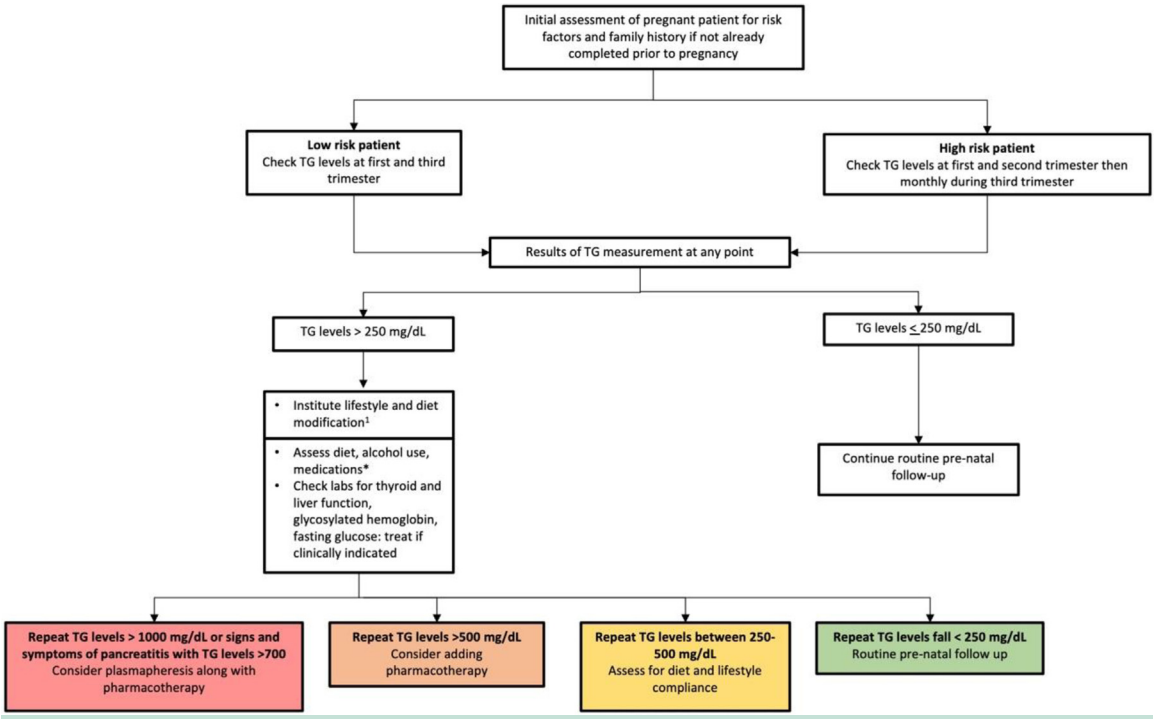

Figure 2 Suggested algorithm for monitoring and treating pregnancy-related hypertriglyceridemia. *Medications that can affect triglyceride levels include antipsychotics, beta-blockers, bile acid sequestrants, contraceptive pills, hormone therapy, thiazides, steroids, retinoids, and protease inhibitors.[1] No fat diet, close weight monitoring, abstain from any alcohol consumption, and exercise as tolerated.

Another case report describes the successful use of early plasmapheresis in the first trimester as treatment for severe hypertriglyceridemia-induced pancreatitis post in -vitro fertilization with no negative side effects noted to the mother or the fetus.[26] This patient had no personal or family history of elevated TG levels but had diet-controlled diabetes and had undergone in vitro fertilization that required ovulation induction with estrogen-related therapy.[26]

CONCLUSION

Our literature search showed that the current management of elevated fasting TG levels during pregnancy is primarily derived from observational data and case reports. The best therapy for pancreatitis in pregnant women who develop hypertriglyceridemia remains its prevention.

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