LIPID CASE 256 Pregnancy and TG Concerns

Lipidologists as well as primary care docs, cards, endos and of course Ob-Gyn docs have to deal with pregnancy issues. I was asked to comment on a 37 year old female. In her 20's she was trying to get pregnant and could not and then her husband died. In the interim she was diagnosed with hypothyroidism and started on therapy. She is remarried now and trying to get pregnant and may need fertility treatments. Here is the problem: She has a very, very strong family history of premature coronary disease: father had MI at age 41 followed by CABG (coronary bypass grafting) and her mother had an MI at age 51 is also post-CABG and stents. The mother has mixed dyslipidemia and hypothyroidism (treated with Synthroid). As if that is not bad enough her brother had an MI at age 42 and then required stents. Apart from lipid medication (see below), the patient's medications are Necon 1/35 28 day (35 mcg ethinyl estradiol and 1 mg norethindrone); Synthroid 0.1 mg daily; fiber 1 tab daily; vitamin B121000 mcg IM prn, multivitamin 1 tab daily; and omega 3 fish oil OTC 3 tabs daily (dose not provided). A recent echocardiogram revealed normal LVEF (LV ejection fraction) and normal LV size; Myocardial Perfusion Imaging (MPI) was negative with respect to Bruce Exercise Treadmill Testing (ETT) for ischemia and the LVEF >70%. BMI, waist size, BP or family history of diabetes not reported.

Her lipid profile on 4/15/09 on Antara (one of the many available fenofibrates) and omega 3 (3 tabs) daily:
TC = 146 HDL-C = 30 LDL-C = 91 TG = 430 Non-HDL-C = 116 LFT's normal (Lipids in mg/dL)

7/1/09 on Crestor 5 mg, omega 3 (3 tabs):
TC = 137 HDL-C = 32 TG = 291 LDL-C = 47 Non-HDL-C = 105 LFT's normal

The clinician commented: "At last visit 2/16/10 she stopped Crestor because she's trying to get pregnant again, but took omega 3 (3 tabs) which are CAT C for pregnancy, but her labs were VERY UNFAVORABLE in our office."

TC = 233 HDL-C could not be measured and LDL-C could not be calculated. TG > 650 LFTs normal. The lipids were repeated at a different lab the same morning with these results:
TC = 200 TG = 843 HDL-C 29 LDL not calculated and TSH was normal at 3.3

The clinician notes: I know Welchol is the only cat B drug I can give her but it is contraindicated in a patient with a TG > 500 mg/dL. He asks how should I advise this patient? Should I have her hold off getting pregnant until TG < 500 then start Welchol thru pregnancy but I don't think that alone will control her TG? Should I put her on Crestor again and try Lovaza?

DAYSPRING ADVICE

A case such as that described is complex and it is crucial to accurately determine the individuals CV risk and presence or absence of atherosclerosis. Once that is done one could determine at what lipid levels to intervene beyond lifestyle advice. Finally one would plan a therapeutic regimen to achieve goal. All of this is significantly complicated by the desire to become pregnant. The work-up described above seems adequate to exclude obvious subclinical atherosclerosis, but some might also suggest doing a CIMT study if available (far cheaper and no radiation). Of course we must keep in mind that many women who present with acute coronary syndromes have normal coronary angiograms and experts recently suggested we stop using the term coronary artery disease in women and start using ischemic heart disease (JACC 2009;54:1561-75). Framingham Risk scoring is also fairly useless in premenopausal (i.e. younger women) women with high and very high TG, but an extreme elevation of a CV risk factor (in this case TG) can elevate someone to the high risk category.

NCEP ATP-III lists the following as known causes of hypertriglyceridemia: 1) Obesity, 2) Physical inactivity, 3) Cigarette smoking, 4) Excess alcohol use, 5) High carbohydrate diet, 6) other diseases (diabetes, nephrosis, hypothyroidism), 7) drugs, 8) Genetic factors. NCEP states that any person not having any of the above is most unlikely to have a TG > 100 mg/dL. NCEP associates TG > 150 with borderline CV risk, a TG > 200 with high CV risk and a TG > 500 with very high risk as pancreatitis is now also at play. The majority of persons with lipid panels like this women are simply insulin resistant, prediabetics. One wonders if her infertility is related to Polycystic Ovarian Syndrome (PCOS) an insulin resistant high androgen state which may be present on top of strong genetic IR traits. If she has IR, her high TG and low HDL-C are likely very indicative of higher CV risk due to a significant increase in apo-B containing lipoproteins (very large VLDLs and especially TG-rich or small LDLs). Since TG-rich and/or small LDLs are cholesterol-depleted they are usually present in very high numbers even in the face of a normal LDL-C. Lipidologists realize the TG-rich VLDLs using cholesteryl ester transfer protein (CETP) swap their TG for cholesteryl ester (CE) within LDLs and HDLs resulting in CE-depleted LDLs and HDLs (explaining the low HDL-C) and CE-rich, TG-poor VLDLs (remnant lipoproteins). Such patients are at higher risk for atherosclerosis and my guess is this scenario is what was going on in her family members. Most clinicians, because of the family history, would check Lp(a) levels in nmol/L not mg/dL (as per NHLBI recommendations: Clinical Chemistry 2003;49:1785–1796) to further help adjudicate her risk: Lp(a) levels would not change the therapeutic approach which is always LDL-C, non-HDL-C or apoB). Finally what are the NCEP ATP-III goals of therapy when treating person with hypertriglyceridemia? It is actually a two-fold approach:

1) If TG are > 500 mg/dL, the first mission is to reduce the TG and risk for pancreatitis using lifestyle and if needed medication with fibrates as initial therapy (since NCEP was published high dose omega-3 FA have also picked up the indication).
2) Once TG are < 500 mg/dL non-HDL-C becomes the recommended goal to reduce CVD. Many do not realize there is absolutely no specific TG goal of therapy in the NCEP guidelines (lack of trial data to support a specific goal). Most folks with high TG have high apoB (LDL-P) and non-HDL-C is simply the “poor man’s” apoB (LDL-P).

Look closely at the first lipid panel while the patient was on fenofibrate and omega-3 FA (3 gm): the patient was actually at NCEP LDL-C and non-HDL-C goal of therapy: thus using NCEP Guidelines there was no need to discontinue the fibrate and switch to Crestor. Of course I would have checked LDL-P once non-HDL-C was normal, because there is considerable (upwards of 30%) discordance between apoB or LDL-P and non-HDL-C in persons with TG/HDL axis disorders. If indeed the apoB or LDL-P was high in the face of normal non-HDL-C then additional therapy is needed and a statin is the appropriate choice (although the fibrate should not have been stopped)

Before we discuss therapeutic approach, let's review the FDA classification of medication safety during pregnancy. First a reminder of the FDA drug categories with respect to use in pregnancy:

Category A: Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B: Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.

Category C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category X: Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

1) So some obvious steps in this patient are to address lifestyle issues very thoroughly including zero alcohol use. A nutritional consult is strongly indicated. I was not provided with waist size or BMI. Close follow up of thyroid treatment is needed: latest TSH is fine. Orlistat (Category B) combined with diet and proper vitamin supplementation is a potential therapy to help lower TG.

2) It is likely, especially if PCOS is present, a TZD like Actos (pioglitazone) a Category C drug or metformin (Category B) will be tried to improve fertility. Both, but especially the former can help lower TG.

3) Because of high estrogen levels, pregnancy is associated with higher TC (25-50%) and TG levels (200-400%) than when the woman is not pregnant: see Clin Lipidol2009;4:91-102 for a fantastic review of pregnancy and lipoproteins. The hormonal changes increase TG production which results in TG-rich VLDLs which upon entering the placenta are exposed to lipoprotein lipase (a powerful triglyceridase). The fatty acids hydrolyzed from the VLDLs can then pass through the placenta and are used for fetal energy. A major worry in the patient at hand is her pre-pregnancy TG levels are in or near the very high risk category. It is possible that the hormonal-induced changes in TG will push the TG to levels associated with acute pancreatitis. Therefore, one should not consider pregnancy until TG are well under 500 (threshold above which pancreatitis becomes a reality). In reality, usually a TG of > 1000 mg/dL or more is needed to precipitate pancreatitis. But a fasting of 500-1000 mg/dL can explode rapidly after certain nutritional excesses or pregnancy. Should gestational diabetes occur, the TG might also rise significantly.

3) So what is the appropriate clinical therapeutic approach? To me the easiest first approach is high dose N-3 fatty acids (Category C). Note in the opening paragraph the provider mentioned OTC omega-3. Please understand no commercially sold omega-3 FA is an OTC product. OTC products are regulated by the FDA. Other than Lovaza, omega-3 products are not and thus they are classified not as OTC meds but rather as food supplements. Their labels may or may not be true as to content or dosage or contaminates. The only FDA-approved N-3 FA is Lovaza. There is also a threshold effect with respect to N-3 FA lowering TG (see superb review by Jacobsen - Am J Clin Nutr 2008;87(suppl):1981S–90S).There is little effect until a dose of 4000 mg is used. Thus this woman has not been receiving the proper dose of N-3 FA. No one can even be sure what amount of N-3 FA were in her non-FDA assayed food supplement tablets. Another major concern with use of an N-3 FA in a woman desiring pregnancy is to use an N-3 product free of all heavy metals. The FDA checks one product for that: Lovaza. Thus if N-3 FA are the desired therapy I would insist that this woman use Lovaza at 4000-6000 mg to get the TG < 500 mg/dL. Fibrates (category C) including gemfibrozil have been used during pregnancy with relative safety. The patient had been on fenofibrate and low dose N-3 FA and did have a TG < 500 mg/dL. So one can consider continued treatment with the fenofibrate or fenofibric acid. Whether one chooses N-3 FA or a fibrate product, if the TG do not get under 500 mg/dL, one can use both. For completeness of discussion, niacin, an effective TG lowering drug when used at high doses (1500-2000 mg) can also be used to reduce TG is a Category C drug.

Once the TG is < 500 mg/dL apoB or LDL-P testing is required. If that is high then CV risk is high. Statins or statin/ezetimibe would be needed with the TG meds. Obviously category X drugs like statins cannot be used during attempted conception period or the pregnancy. There is little knowledge about ezetimibe (category C) during pregnancy, but it is not category X and is an

option if apoB is a problem. Because of the very high TG bile acid sequestrants should not be considered even though they are category B. Since this woman has passed the tests looking for subclinical atherosclerosis even if the apoB or LDL-P is high I think it is reasonable to go with the N-3 FA and fibrates as TG lowering therapies to minimize pancreatitis risk and not worry about apoB and CAD events for the next year or two. TG must be closely monitored during any pregnancy in such a woman. Should it ever happen, even during pregnancy, emergency treatment of severe hypertriglyceridemia and pancreatitis is plasmapheresis. Lastly, before pregnancy is attempted her husband should be screened for lipid disorders and genetic counseling is indicated. This patient and her husband must be fully educated on the risk and effects of acute pancreatitis during pregnancy, including death.