LIPID CASE 267 Hormones Lipids and Lipoproteins?

On to the case: I was asked about the following patient which will lead into a discussion of using menopausal hormone therapies in women with CV risk. A physician inquired about a 45 year old Asian Indian-American woman who went through premature menopause at age 43 years and now has severe atrophic vaginitis. She has a family history of premature coronary artery disease and has the metabolic syndrome, despite a normal BMI of 18.8 (for Asio-Pacific classification).

Her serial lab numbers are as follows: all lipid concentrations in mg/dL

In 04/2010: on metformin 500 mg once daily
Fasting blood sugar = 113 mg/dL, HbA1c = 5.9% hs-CRP = 0.35 mg/dL (low)

TC = 224, TG = 229, HDL-C = 52, LDL-C = 126, VLDL-C = 46, Non-HDL-C = 172
Remember using the Friedewald formula VLDL-C = TG/5.
LDL-C = TC - [HDL-C + VLDL-C]
Non HDL-C = TC - HDL-C or = LDL-C + VLDL-C
Follicle stimulating hormone: FSH 118 (high and consistent with menopause)

Her lifestyle included carbohydrate moderation and she actually lost more weight and then went off metformin. She started on both the selective estrogen receptor (SERM) Evista (raloxifene) 60 mg daily as well as Premarin vaginal cream.

Her follow up labs in July/2010:
HbA1c = 6.1%,

TC = 199, TG =145, HDL-C = 51, LDL-C =119, VLDL-C = 29, Non-HDL-C = 148

The patient then stopped Evista and wanted to be on Hormone Replacement Therapy (HRT) secondary to severe menopausal syndrome and she was switched to estradiol 0.5 mg daily and Provera (medroxyprogesterone acetate or MPA) 2.5 mg daily. On HRT her labs in 10/2010 are as follows:

FBS 111,
TC = 266, TG = 197, HDL-C = 54, LDL-C = 173, VLDL-C = 19, non-HDL-C = 212
An NMR (nuclear magnetic resonance spectroscopy or NMR LipoProfile) was also done:
Total LDL-P = 2418 nmol/L (very high risk: the 99th percentile population cut point)
Small LDL-P = 1344 nmol/L (elevated)
HDL-P = 37.8 (excellent)
Lipoprotein associated phospholipase A2 (Lp-PLA2 or PLAC test) was normal at 134, hs-CRP remained low at 0.27 mg/dL

The clinician commented that the patient likely has Type IIb lipid phenotype (using the 1967 Fredrickson's, Levy and Lees classification) and recommended that the HRT regimen be changed to estradiol .5 mg day 1 to 21 and Provera (MPA) 2.5mg day 14 to 28. The patient was also started on Simcor (extended release niacin or Niaspan with

simvastatin) to be titrated to 1000/40. A CT for coronary calcium score was also advised. Of course I was asked for my take on this case including the impact of HRT.

DAYSPRING DISCUSSION:

Let's examine the medical history and first set of labs and pretend we were back in 2001 with the brand new NCEP ATP-III guidelines. Since she does not have two major risk factors for CHD (all she has is a family history) she does not qualify for Framingham Risk Scoring (FRS). Her ten years risk of a hard CV event is low. Her LDL-C is well below the goal of 160 mg/dL and the optional goal of 130 mg/dL. However her TG are > 200 mg/dL and thus one could say her non-HDL-C is above the optional goal of 160 mg/dL. She does not qualify for the metabolic syndrome which would increase her risk (she has only two criteria). She was given metformin to delay T2DM onset (an off-label use), but the dose used was likely too low. Clearly without using lipoprotein quantification we are going nowhere in our attempts to reduce CV risk in this woman.

The reality is she certainly looks like a typical IR menopausal woman with a TG/HDL axis disorder with presumably significant hyperbetalipoproteinemia due to the presence of TG-rich lipoproteins. The IR is also highly genetic in both Asian and American Indians. Asian Indians also have a Lp(a) issues so I would be sure to also check Lp(a) mass and Lp(a)-cholesterol.

With respect to menopausal therapies, I not sure what the indication for Evista was unless she had osteopenia or fracture risk or breast cancer risk with no quality of life (QOL) issues. If she has not had a BMD, it should be done. Evista would also certainly help lower apoB by 10-15% (see Dayspring T, et al. Effects of raloxifene on lipid and lipoprotein levels in postmenopausal osteoporotic women with and without hypertriglyceridemia, Metabolism Clinical and Experimental 2006;55:972-979). The proper treatment for atrophic vaginitis is indeed local (not systemic) estrogen although I would have stayed away from the Premarin preparation (formerly called conjugated equine estrogen, but now simply called conjugated estrogen). No one actually knows exactly what molecules are in that preparation: certainly not the manufacturer or FDA). I prefer to use Vagifem tablets (estradiol) 10 mg (a new low dose formulation): one tab daily for two weeks then twice weekly thereafter.

Unless she continues her aggressive lifestyle she will likely need metformin (if tolerated) at a much higher dose than 500 mg daily) or other insulin sensitizer to delay T2DM onset (so prevalent in her ethnic group). Got to preserve those beta cells. Interestingly 20% of full blown metabolic syndrome patients have a BMI < 26 (NHANES data).

Although the HgbA1c had increased to 6.1% (off metformin), the second lipid profile (July) was improved with reductions in TG, VLDL-C, LDL-C and non-HDL-C. So all of the NCEP ATP-III believers would again be congratulating themselves. A lipoproteinologist like myself basically knows that until proven otherwise we should assume, no matter what the lipid profile shows the patient likely has an elevated concentration of atherogenic apoB (particles: almost all of which are either large TG-rich, cholesteryl ester (CE)-poor LDLs or small (CE-poor) LDLs). In general in

menopause due to the absence of estrogen (an insulin sensitizer), fat redistribution (from butt to gut), and age itself, there is a worsening of IR: with subsequent increased hepatic TG, increased large VLDL-P and elevated LDL-P (please see Dayspring TD & Pokrywka G, The Impact of Triglycerides on Lipid and Lipoprotein Biology in Women. Gender Medicine 2010;7:1-17 This paper also discusses the effects of hormonal therapies on lipids).

Let's get back to the menopausal therapeutic decisions. First begin with using the correct terminology. If you have not seen it get a hold of the free North American Menopause Society 2010 Position Statement on Hormonal Therapy (Menopause 2010;17:242-255: see http://www.menopause.org/PSht10.pdf).

This woman had menopause at age 43: that is not considered premature menopause, but rather early menopause. Premature menopause is the cessation of menses before age 40. Early menopause is the time period of five years after the last menstrual episode (natural or induced). Perimenopause is the period starting as early as a few years prior to the final menstrual period (FMP) up until 12 months after the FMP.

Progestogen = either progesterone (the natural progestogen) or a progestin (synthetic progestogen)
EPT = estrogen + progestogen therapy
ET = estrogen only therapy
HT = Hormone therapy (encompassing ET and EPT)
Local therapy: vaginal ET that does not cause a systemic increase in estrogen levels
available as tablets, cream or rings
Systemic therapy: does raise estrogen blood levels
available as oral tabs, several types of dermal applications, vaginal
HRT (hormone replacement therapy) should no longer be used

However the 2010 Endocrine Society Postmenopausal Hormone Therapy Guidelines (J Clin Endo 2010;95(suppl):S1-S66) which is also must reading for anyone counseling a menopausal woman, advocate the following terms

ET = estrogen only therapy EP = estrogen + progestogen therapy
MHT: Menopausal Hormone Therapy = any type of HT used during menopause.
They believe MHT should replace HRT.

More from the NAMs statement:

Progestogens are available as tablets or capsules, vaginal gel, or in an IUD (Mirena)

EPT can be administered:
Oral continuous-cyclic.
Oral continuous combined
Oral intermittent - combined
Transdermal continuous-combined
Transdermal continuous with oral progestogen

For a complete, extremely useful listing (downloadable as a pdf) of all HT products and doses available in the US please go to http://www.menopause.org/htcharts.pdf

Menopausal HT has one FDA indication and that is to address the quality of life issues (of which there can be many). Although not to be used as an initial therapy except under special circumstances, estrogen also is an excellent therapy to keep a female skeleton intact. Since most of the vaginal ETs do and oral or transdermal systemic HT does not address atrophic vaginitis, a local nonsystemic vaginal estrogen should be continued (Vagifem 10 mg as discussed above would be my choice). Estradiol, is the estrogen I usually prefer (that is the hormone made by the ovaries). Of course there are other available estrogen molecules apart from estradiol. There are many ways to administer ET (vaginally at low or, high dose, topical as a gel or transdermal patch), but oral is the easiest and most preferred. Since the patient has a uterus, a progestogen must be prescribed to prevent estrogen-induced uterine cancer. Unfortunately EPT increases breast cancer risk compared to ET (not associated with breast cancer in WHI), but nowadays most providers use low dose, short term EPT.

Note in July the clinician stated there were severe menopausal symptoms. I have to ask were they induced by the raloxifene (Evista)? If so simply stopping that medication might suffice. I suspect the symptoms were already there which begs the question why Evista was started in the first place. Not only does Evista have the potential to worsen vasomotor flushes it also can be associated with or aggravate atrophic vaginitis (note it is possible to coprescribe local vaginal ET when a women is on Evista).

In this case under discussion I would also have stopped the Evista and prescribe systemic estrogen (note there are vaginal products (Femring) that also increase systemic estrogen and can help both vaginal and systemic estrogen deficiency issues. Since this woman has a uterus she needs a progestogen. I discourage use of Provera (Medroxyprogesterone acetate) although the patient was using the low dose. Provera is too androgenic, not kind to the breast when combined with ET, and like many drugs with androgenic activity, it has a potential negative HDL effect. For this patient's severe quality of life issues, I'd prefer using a combination product using estradiol and norethindrone acetate (NETA): namely Activella which is a unique combined continuous estrogen/progestin containing estradiol with the androgenic (dose dependent) progestin NETA. It is available as the standard 1 mg estradiol / 0.5 mg NETA tablet or a low dose formulation with estradiol 0.5 mg / 0.1 mg NETA). At the standard dose (1/0.5 mg formulation) it is the only menopausal HT that can lower apoB). The reason this product makes sense is that the androgenic progestin (NETA) at the 0.5 mg dose can lower TG (which leads to the apoB reduction). Despite its androgenicity, the 0.5 mg dose of NETA has no statistically significant effect on HDL-C when combined with 1 mg of estradiol (standard dose Activella). If used alone a 1 mg dose of estradiol increases HDL-C and HDL-P (although we have no idea what it does to HDL functionality) but it would also raise TG. When given as the combo product with 0.5 mg of NETA, there is TG lowering with a neutral HDL-C effect and an apoB lowering effect (Arch Intern Med. 2000;160:3315-3325*)*. Of course, we should start HT therapy at the lowest possible dose which means the Activella 0.5/0.1 formulation. This formulation probably has no lipid/lipoprotein benefit or

adversity, but might be good for her QOL issues and her bones. The dose could be increased if the QOL issues were not abated. Do not confuse Activella with FemHRT which uses ethinyl estradiol plus NETA - very different effects on lipids and lipoproteins (at the standard strength it reduces HDL-C and no lowering of apoB)

If you did not want to go with a combined/continuous oral or transdermal (see Combipatch, or Climara Pro) product (bleeding or skin issues) then individual titration of lower dose estradiol (orally or transdermally using Vivelle dot) along with progesterone (the ovarian secreted progestogen) which is sold as Prometrium capsules makes the most sense. Prometrium can be given at a lower dose if used every day (combined continuous), or in a higher dose if used cyclically (last two weeks of cycle). Progesterone is neutral on lipids and lipoproteins. Transdermal estradiol or low dose oral estradiol is lipid neutral if combined with Prometrium. Higher oral doses of estradiol can raise TG but not usually apoB.

So I would switch this woman to low dose Activella. NOTE: HT should not be used to prevent or reduce atherothrombotic events. If you are using HT in an at risk women, be sure to treat all CV risk factors aggressively. However, in my mind too many clinicians including internists, FPs, Cards and even endos automatically deny **symptomatic** women an excellent therapy (HT) if they have CV risk. Please note that in the Heart and Estrogen/Progestin replacement Study (HERS) there was no HT (Prempro) related risk in the women with CHD who also were on statins. Interestingly in that study women on HT who also used ASA or statins had 50% less DVT complications.

Now back to the lipids: Finally in October, lipoproteins were assayed using NMR. The lipid profile had deteriorated and the NMR confirmed my suspicions that she has extremely severe hyperbetalipoproteinemia. Her LDL-P is at the 99th percentile population cut point (she is worse than virtually everyone). So it is time to get serious with her lipoprotein-modulating therapy.

The clinician raised the possibility of doing a coronary calcium score. I think she is too young to consider that: one is not likely to see much and even if negative her CV risk based on the metabolic workup is horrific (in view of the extreme LDL-P I now consider her to be high risk) and the CAC would not change my treatment recommendations. Remember 50% of women with chest pain presenting with ACS do not have obstructive CAD - we now advised to refer to the disease state in women as ischemic heart disease instead of coronary heart disease (J Am Coll Cardiol 2009;54:1561–75). Also upwards of 20% of folks with zero CAC can have an event over the next 4 years. Indeed total coronary occlusion frequently occurs in the absence of any detectable calcification. (Circulation. 2008;117:1693-1700 and J Am Coll Cardiol 2010;55:627–34).

There is little prayer to get the very high LDL-P to goal with statin monotherapy (Journal of Clinical Lipidology (2008) 2, 36–42). The provider suggested switching to Simcor (simvastatin plus extended-release niacin or Niaspan). Indeed the ADA/ACCF guidelines on lipoprotein management in patients with cardiometabolic risk, list niacin as the preferred add on to a statin. However the key to good menopausal healthcare is that the provider must individualize all therapies to the specific woman. So I ask, why go to

niacin in a woman with severe vasomotor flushes who has no CAD present, who has a normal HDL-C and a perfectly normal HDL-P, as well as terrible insulin resistance. I do not see any major indication for niacin at this stage of the game. She certainly needs aggressive LDL-P lowering beyond what a statin can do. Since PM women tend to over absorb cholesterol and noncholesterol sterols, statin + ezetimibe (because of the sterol hyperabsorption might be a better first statin add-on choice. The high HDL-C in the face of elevated TG (one would normally expect HDL-C to be low) also suggests over absorption of cholesterol. Statin + ezetimibe is usually more potent in reducing apoB or LDL-P than is statin + niacin (because although niacin does lower total LDL-P (Total LDL-P = small LDL-P + large LDL-P) niacin actually increases large LDL-P while reducing small LDL-P so the effect on total LDL-P is not as great. The LDL-P in this woman is probably too high for Vytorin 40 although it could be tried (would save a copay compared to statin + separate Zetia Rx). I almost never use simvastatin 80 mg or Vytorin 80 because of the myopathy risk). Since she has maxed out lifestyle, I really suspect she will need Crestor 20-40/Zetia.

One other thought: She is insulin resistant - and her statin needs help to get LDL-P to goal. How about adding the bile acid sequestrant colesevelam which can generate additional LDL-P lowering on top of a statin and also has an FDA approval to reduce HgbA1c (hers is 6.1%). Welchol also can be combined with metformin which perhaps is an ideal combo as the sequestrant minimizes the possible loose BMs seen in some who use metformin (see Arch Intern Med. 2008;168(18):1975-1983). Welchol is available as tablets (6 per day), but also as a much more convenient to use powder for suspension (3.75 mg) is used once daily. We have recently learned that the glycemic benefits of colesevelam are not mediated through FXR or LXR (as previously believed) but rather through inducing glucagon like protein 1 (GLP-1) secretion (which helps insulin action without causing hypoglycemia and will suppress glycogenolysis). For perhaps the best reason of all to consider lifelong colesevelam check out reference 5 below - I think I'd rather keep my ileum and use a sequestrant instead.

If you found this discussion of menopausal issues fascinating or new - please consider joining the North American Menopause Society of which I am so proud to be a not only a member but also a Certified Menopause Practitioner. www.menopause.org