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Clinical Lipidology Roundtable Discussion

JCL roundtable: Cardiovascular disease risk reduction in menopausal women

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Abstract: Ovarian failure occurs in most women during the late fifth decade or early sixth decade of life. This causes a number of changes in physiology as estrogen and progestin concentrations decline. These involve lipoprotein metabolism and the vasculature. The risk factors for large vessel disease increase, and dysfunction of the small resistance vessels responds with changes in blood flow to the skin causing unpleasant symptoms. These and other changes result in visits to the physician. A reassessment of risk factors and symptoms is needed to develop a new plan for effective management, both short term and long term.

Ovarian failure occurs in most women during the late fifth decade or early sixth decade of life. This causes a number of changes in physiology as estrogen and progestin concentrations decline. These effects involve lipoprotein metabolism and the vasculature. The risk factors for large vessel disease increase, and dysfunction of the small resistance vessels responds with changes in blood flow to the skin causing unpleasant symptoms. These and other changes result in visits to the physician. A reassessment of risk factors and symptoms is needed to develop a new plan for effective management, both short term and long term.

We are joined for this Roundtable discussion by 2 clinical specialists, Dr Martha Gulati from the University of Arizona-Phoenix and Dr Gina Lundberg from Emory University School of Medicine. Both have academic and clinical interests in vascular disease in women. They have agreed to discuss with me, the factors of major concern in contributing to the rates of clinical vascular disease in women. The focus will be on lipoproteins as risk factors and their change at the time of the menopause.

Dr Brown: Dr Gulati, would you review the important plasma lipid levels that might relate to vascular disease in women as compared with men?

Dr Brown

Dr Martha Gulati: Premenopausal women, have higher mean levels of high-density lipoprotein cholesterol (HDL-C) and lower high-density lipoprotein cholesterol (LDL-C) levels, lower very LDL (VLDL) cholesterol, and triglyceride levels than their male counterparts, age adjusted. Once they approach the perimenopausal stage, LDL-C and the VLDL values increase. However, the HDL-C falls.

Dr Gulati

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Dr Lundberg

Dr Gina Lundberg: After menopause, women have an increase in their apolipoprotein B (ApoB) containing lipoproteins in general. In women who have the inherited higher concentrations of the Lp(a) lipoprotein, these also increase after menopause. In those with diabetes mellitus, there is a worsening of their dyslipidemia with a greater decrease in HDL-C, greater increase in triglycerides and in the LDL particle number with a decrease in LDL particle size.

Dr Brown: Our observational studies clearly indicate that vascular disease is quite uncommon in women before the seventh decade of life. This usually follows the menopause for most women by at least a decade. However, this seems to have led to the concept that functional ovarian hormones are protective. Is there evidence that it is the ovarian failure which causes changes in lipoprotein metabolism that might be causative in the development of vascular disease?

Dr Gulati: I think it's a little bit confounded by the things that happen to women at the same time. Women with premature ovarian failure have an increased risk of premature cardiovascular disease (CVD). Women with polycystic ovarian syndrome are at an increased risk of developing the metabolic syndrome also. They are therefore at increased risk of diabetes and CVD. It is not just the changes in the hormones but also changes in the lipid profile that occur concomitantly that seems to accelerate the risk. Similarly, when a woman goes through menopause, we see the same changes to lipids as seen in those with premature ovarian failure. As a result, it is hard to separate the impact of changes in the sex steroid levels from other changes (weight gain, central obesity, fat distribution, physical inactivity, and aging) that are occurring at that time.

Dr Brown: It seems noteworthy that men will go through a very similar sequence of changes but these usually start in the mid-30s with an increase in the abdominal fat mass, in plasma triglycerides, and often an increase in LDL-C. This rise in blood lipids reaches its peak in most men by their mid to late 40s. This change seems similar to that observed in women but it occurs 10 15 years or earlier. This difference in the timing of lipid changes with age corresponds very closely to the interval before the onset of clinical vascular disease in both men and women. Metabolic changes are evident about 20 to 25 years before vascular events in both genders.

One of the very worrisome issues that has become obvious in the last 30 years is the rising stroke rates in women. Total stroke rates and stroke death in women now exceeds that in men. Are there stroke risk factors that are particularly important in women?

Dr Lundberg: Well I would say that the increased risk of stroke in women is more than just a lipid problem. There's more hypertension in older women and there is more atrial fibrillation in older women. We know from studies that women are less often prescribed an anticoagulant for atrial fibrillation. Women are less often prescribed aspirin and statin therapy.

There are other confounding factors that go along with gender-specific issues. Women tend to have more migraine headaches with aura and more inflammatory illnesses like lupus and rheumatoid arthritis, which are risk factors for stroke. In younger women, stroke can be a complication of pregnancy. Women who have had pre-eclampsia, eclampsia, hypertension with their pregnancy, or gestational diabetes have increased risks for stroke and CVD. So I think there are multiple reasons that strokes are more common in women.

Dr Gulati: There are additional sex-specific issues, particularly in young women. Women who are taking oral contraceptives are at higher risk for stroke. This is most obvious in women who smoke and are on birth control pills. This is also true in the younger women who have hypertension and are placed on oral contraceptives. In older women, hormone replacement therapy (HRT) is associated with an increase in the risk of stroke. The prevalence of stroke is actually higher in younger women than in men of the same age. So important risk factors for stroke are active in women and these are not restricted to older women.

Dr Brown: So the disconnect between stroke and other manifestations of arterial disease begins earlier in life than has seemed evident? The relative risk of a heart attack in men is significantly higher but the risk of a stroke is comparable or even higher throughout life. Is that correct?

Dr Gulati: That's correct.

Dr Brown: Let's turn to the issue of HRT as a common occurrence in dealing with menopausal symptoms. The indication for its use in the prevention of vascular disease seems to have been markedly reduced by convincing evidence from clinical trials of more harm than benefit. So what is the appropriate use of hormonal therapy and what do we expect to see when we use it with regard to lipid levels?

Dr Gulati: From observational studies, we really thought that postmenopausal hormone replacement would continue this intrinsic benefit that was seen in younger premenopausal women who had a lower risk of heart disease when compared with the same aged men. And observational studies would support that. But then when randomized controlled trials were started, no study supported a reduction in heart disease in those given hormone replacement compared with placebo. The first of these was the Heart and Estrogen/Progestin Replacement Study (HERS). HERS found that the use of estrogen plus progestin in postmenopausal women with heart disease did not prevent further heart attacks or death from coronary heart disease (CHD). This occurred despite the positive effect of treatment on lipoproteins (LDL-C was reduced by 11% and HDL-C was increased by 10%). But HERS was a secondary prevention trial because the presence of CVD was