ARIC Manuscript Proposal # 837

PC Reviewed: 10/16/01	**Status: __A__**	**Priority: ___2_**
SC Reviewed: 10/17/01	**Status: __A__**	**Priority: ___2_**

1.a. Full Title: Correlation Between Endogenous Post-menopausal Hormones and Lipids: The Atherosclerosis Risk In Communities Study

b. Abbreviated Title (Length 26 characters): Hormones and Lipids

2. Writing Group (list individual with lead responsibility first):

Lead: Sherita Hill Golden, MD, MHS
Address: Division of Endocrinology and Metabolism
Johns Hopkins University School of Medicine
1830 E. Monument Street
Suite 333
Baltimore, MD 21205

Phone: 410-955-3921 Fax: 410-955-8172
E-mail: sahill@jhmi.edu

Writing group members: Moyses Szklo, MD, DrPH, Jingzhong Ding, MD, PhD, Ann Maguire, MD, MPH, Jane A. Cauley, DrPH, Adrian S. Dobs, MD, MHS

3. Timeline: Analyses to begin immediately

4. Rationale:

Several studies have shown beneficial effects of exogenous estrogen replacement therapy on blood lipid levels in post-menopausal women, including increased HDL-cholesterol and lower LDL-cholesterol (1-4). Only a few studies have examined the relationship between endogenous post-menopausal hormones and lipid levels in women not taking hormone replacement therapy. Sex hormone binding globulin (SHBG) has been shown to be positively associated with HDL (5-7)and negatively associated with triglycerides (6;7). No correlation has been demonstrated between estrone and estradiol levels and lipids (8). Studies of the relationship between DHEA and DHEAS and lipids have yielded conflicting results, with some studies demonstrating a less atherogenic lipid profile (9-12), and others demonstrating a more atherogenic profile (13). One study in men examining Lipoprotein(a) showed no association with total or free testosterone, estradiol, DHEAS, or SHBG (14). In a cross-sectional study in peri-menopausal women, Shelley et al. found that in multivariate analysis, free androgen index was positively associated with LDL, but only among women with a low body-mass index (15). In this study, there was no relationship between estradiol and HDL, LDL, or triglycerides in multivariate analysis. We are not aware of any studies examining the relationship between Lp(a) and hormone levels in post-

menopausal women. One study examining the relationship between diastolic blood pressure endogenous hormone levels in the peri-menopausal period failed to find an association (15).

5. Main Hypothesis/Study Questions:

Are there correlations between endogenous hormone levels and lipid levels in post-menopausal women not taking hormone replacement therapy?

6. Data (variables, time window, source, inclusions/exclusions):

Our analysis will be based on a subset of post-menopausal women in ARIC who were a part of a case-control study designed to look at the relationship between endogenous post-menopausal hormone levels and carotid atherosclerosis. In the original case-control study, cases were 182 post-menopausal women not taking hormone replacement therapy whose mean carotid IMT was >95th percentile for the six sites visualized. Controls were 182 post-menopausal women not taking hormone replacement therapy whose mean carotid IMT was <75th percentile for the six sites visualized. Cases and controls were frequency matched on age (in 5-year intervals) and ARIC field center (as a proxy for race).

Hormone variables from Visit 2 measured in the case-control study that are available for the present analysis include estrone, androstenedione, dehydroepiandrosterone-sulfate (DHEA-S), total testosterone, and SHBG. The free androgen index can be calculated as the ratio of total testosterone/SHBG.

Lipid variables from Visit 2 available to be included in the analysis are total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides, and Lp(a).

Visit 1 variables to be included in analysis: age, ARIC center, smoking history, alcohol use, sports index, body-mass index, insulin level, cholesterol medication use, presence of diabetes, fasting serum glucose, systolic blood pressure, and diastolic blood pressure.

Analyses will include multiple linear regression to determine the correlation between endogenous hormone levels and lipid parameters. In addition, the mean values of each lipid parameter will be estimated for each quartile of estrone, androstenedione, DHEA-S, SHBG, and total testosterone, using multiple linear regression. Because one group of participants were selected for presence of significant carotid atherosclerosis and the other groups was selected for the presence of minimal carotid atherosclerosis, we will tests for heterogeneity in the relationship between hormone levels and lipid levels to determine whether the two groups should be analyzed separately.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _x___ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? **____ Yes _x___ No**

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"? **____ Yes ____ No**

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

___x___ Yes _____ No

Reference List

(1) Manolio TA, Furberg CD, Shemanski L, Psaty BM, O'Leary DH, Tracy RP et al. Associations of postmenopausal estrogen use with cardiovascular disease and its risk factors in older women. The CHS Collaborative Research Group. Circulation 1993; 88(5 Pt 1):2163-2171.

(2) Nabulsi AA, Folsom AR, White A, Patsch W, Heiss G, Wu KK et al. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. The Atherosclerosis Risk in Communities Study Investigators [see comments]. N Engl J Med 1993; 328(15):1069-1075.

(3) Vaziri SM, Evans JC, Larson MG, Wilson PW. The impact of female hormone usage on the lipid profile. The Framingham Offspring Study [see comments]. Arch Intern Med 1993; 153(19):2200-2206.

(4) Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial [see comments] [published erratum appears in JAMA 1995 Dec 6;274(21):1676]. JAMA 1995; 273(3):199-208.

(5) Masarei JR, Armstrong BK, Skinner MW, Ratajczak T, Hahnel R, Crooke D et al. HDL-cholesterol and sex-hormone status. Lancet 1980; 1(8161):208.

(6) Soler JT, Folsom AR, Kaye SA, Prineas RJ. Associations of abdominal adiposity, fasting insulin, sex hormone binding globulin, and estrone with lipids and lipoproteins in post- menopausal women. Atherosclerosis 1989; 79(1):21-27.

(7) Haffner SM, Dunn JF, Katz MS. Relationship of sex hormone-binding globulin to lipid, lipoprotein, glucose, and insulin concentrations in postmenopausal women. Metabolism 1992; 41(3):278-284.

(8) Cauley JA, Gutai JP, Kuller LH, Powell JG. The relation of endogenous sex steroid hormone concentrations to serum lipid and lipoprotein levels in postmenopausal women. Am J Epidemiol 1990; 132(5):884-894.

(9) Nafziger AN, Jenkins PL, Boslin SJ, Pearson TA. Dihydroepiandrosterone, lipids and apoproteins: associations in a free living population. [Abstr.]. Circulation 1990; 82(Suppl III):469.

(10) Sonka J, Fassati M, Fassati P, Gregorova I, Picek K. Serum lipids and dehydroepiandrosterone excretion in normal subjects. J Lipid Res 1968; 9(6):769-772.

(11) Lopez SA, Wingo C, Herbert JA, Johnson WK, Troendle DA. Total serum cholesterol and urinary dehydroepiandrosterone in humans. Arteriosclerosis 1970; 24:471-481.

(12) Aldercreutz H, Kerstell J, Schaumann KO, Svanborg A, Vihko R. Plasma lipids and steroid hormones in patients with hypercholesterolaemia or hyperlipaemia during dehydroepiandrosterone sulfate administration. European Journal of Clinical Investigation 1972; 2:91-95.

(13) Herrington DM, Gordon GB, Achuff SC, Trejo JF, Weisman HF, Kwiterovich PO, Jr. et al. Plasma dehydroepiandrosterone and dehydroepiandrosterone sulfate in patients undergoing diagnostic coronary angiography. J Am Coll Cardiol 1990; 16(6):862-870.

(14) Haffner SM, Mykkanen L, Gruber KK, Rainwater DL, Laakso M. Lack of association between sex hormones and Lp(a) concentrations in American and Finnish men. Arterioscler Thromb 1994; 14(1):19-24.

(15) Shelley JM, Green A, Smith AM, Dudley E, Dennerstein L, Hopper J et al. Relationship of endogenous sex hormones to lipids and blood pressure in mid-aged women. Ann Epidemiol 1998; 8(1):39-45.