ARIC Manuscript Proposal # 991

PC Reviewed: 01/20/04	**Status: A**	**Priority: 2**
SC Reviewed: 01/20/04	**Status: A**	**Priority: 2**

1.a. Full Title:
Relation of Reproductive Factors to Type 2 diabetes mellitus and cardiovascular disease

b. Abbreviated Title (Length 26 characters):
Reproductive factors, diabetes, and cardiovascular disease

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

Lead: Wanda Nicholson, MD, MPH
Address: 600 North Wolfe Street/Harvey 319
Baltimore, MD 21287

Phone: 443-287-6942 Fax: 410-502-5994
E-mail: wnichol@jhmi.edu

Writing group members:
Neil Powe, MD, MPH, MBA (Senior author)
Josef Coresh, PhD
James Pankow, PhD and others as he designates
Fred Brancati, MD, MHS
Sherita Golden, MD
Jessica Yeh

3. Timeline:
7/04-6/06

4. Rationale:

Previous studies have suggested an association between parity and subsequent development of Type 2 diabetes mellitus and cardiovascular disease. Moreover, the association between parity, hysterectomy with ovarian conservation and coronary heart disease remains controversial. We propose to 1) determine the association of parity with incident Type 2 diabetes mellitus; 2) determine the relation of parity to lifestyle behaviors and incident cardiovascular disease, and 3) examine the relation of parity and hysterectomy alone with cardiovascular disease among African-American and white women. *These analyses address the effect of childbearing and other reproductive factors on subsequent development of Type 2 diabetes and cardiovascular disease.*

Parity and Type 2 diabetes mellitus

Parity is generally defined as the number of live births, spontaneous abortions (miscarriages), and induced abortions (elective terminations) during a woman's reproductive life span. While parity was first proposed to explain the excess prevalence of diabetes in women in

1956, the relationship between parity and the risk of diabetes remains unclear. Several studies have found a positive association between increasing parity and Type 2 DM. O'Sullivan found that the age-adjusted probability of Type 2 DM increased from 1% in women with 0-1 births to 2.3% in women with 4-5 births. Kritz-Silverstein and colleagues found that one or more births was associated with a 1.2 greater odds of Type 2 DM (Odds ratio (OR) 1.2; 95% confidence interval (CI) 1.1-1.3) and impaired glucose tolerance (OR 1.1; 95% CI 1.01-1.2), even after adjustment for obesity and socio-demographic factors. However, these studies were primarily based on prevalence data. In addition there was little data on race-specific associations between parity and Type 2 DM. Further, adjustment for lifestyle behaviors was limited. In unadjusted analysis from ARIC, increasing parity was associated with both race and Type 2 diabetes. *We propose to determine the association of parity with incident Type 2 diabetes mellitus after adjustment for potential confounders, including race, age, body mass index, and lifestyle factors (diet, physical activity).*

While early investigations hypothesized that multiple exposures to the metabolic changes of pregnancy accounted for this relationship, no specific mechanisms were proposed. Several analyses focus on the effect of parity on insulin resistance and β-cell dysfunction to better understand the association between parity and Type 2 DM. Increasing parity was associated with insulin resistance, as evidenced by elevated fasting insulin levels, in several analyses. Because parity has been shown to be associated with insulin resistance and C-reactive protein is associated with both inflammation and insulin resistance, we hypothesize that 1) increasing parity is associated with elevated C-reactive protein levels; and 2) the association of parity with Type 2 DM is mediated by inflammation (e.g. CRP). *In a subgroup analysis using ancillary data from Pankow and others, we propose to first determine the association of parity with C-reactive protein levels. We then propose to determine if the association between parity and Type 2 DM is mediated by inflammation (as evidenced by C-reactive protein)*. If the addition of C-reactive protein levels attenuates the relation of parity to Type 2 diabetes, the analysis will suggest that inflammation does function as a mediator. If the addition of C-reactive protein levels does not affect the relation of parity with Type 2 DM, the analysis will suggest that parity is associated with Type 2 diabetes through so other mechanism.

Parity and Cardiovascular Disease

Several studies have examined the association between increasing parity and cardiovascular disease and have found conflicting results. Investigators hypothesize that insulin resistance and changes in lipid metabolism during pregnancy place multiparous women at greater risk of subsequent CHD. Several of these studies, however, have been limited by a relatively small number of incident coronary events and lack of adjustment for specific cardiovascular risk factors. Moreover, there is continued debate as to whether the relation of parity to CHD is due directly to biological mechanisms or rather, to lifestyle behaviors related to multiple childbearing. Lawlor and colleagues examined CHD cases in a large study of men and women in Britain. They found that the number of children was positively associated with body mass index in both men and women and with diabetes in women. Among male and female participants with at least 2 children, each additional child increased the age-adjusted odds of CHD by 30%. After adjustment for demographic and lifestyle behaviors, the association of parity with CHD was attenuated in men after, but remained moderately associated with CHD in women. *We propose to determine the presence and magnitude of association of parity with cardiovascular*

disease among African-American and white women, after adjustment for lifestyle factors, including dietary habits and physical activity.

Parity, Prior Hysterectomy, and Cardiovascular Disease

Hysterectomy is one of the most common surgical procedures performed in the United States. Recent data show that approximately 550,000 hysterectomies for benign disease are performed annually. While public interest has focused primarily on geographical variations and the effect of patient-provider relationships on hysterectomy, there is little data on the long-term health effects of hysterectomy. Several early studies found an increased risk of coronary heart disease in women who had undergone hysterectomy with and without the removal of one or both ovaries. The Framingham Study, for example, found an increase in the incidence of CHD independent of whether the ovaries were removed or conserved. Palmer and associates found an elevated risk of myocardial infarction in women who had had a hysterectomy prior to age 45 with or without both ovaries removed.

Cessation of estrogen production is the proposed mechanism for the development of CHD in women who undergo hysterectomy + removal of both ovaries. For women who undergo hysterectomy with conservation of one or both ovaries, investigators have proposed that the lack of prostacyclin secretion (a known vasodilator) from the uterus leads to vascular changes and cardiovascular disease. Luoto and colleagues found an increased risk of hypertension (Odds ratio 2.2; 95% Confidence Interval 1.5-3.1) in women who had undergone hysterectomy with ovarian conservation compared to women who had not undergone hysterectomy after adjustment for age, age at hysterectomy, other cardiovascular risk factors, and use of hormone replacement therapy. This study, however, was based on prevalent, rather than incident CHD. Further, despite the excess prevalence of hysterectomy among African-American women, there is limited race-specific data on the relation of hysterectomy and cardiovascular disease. *We propose to compare the incidence of cardiovascular disease (*coronary heart disease, hypertension, abnormal lipid profile*) in women with a history of hysterectomy* (hysterectomy alone or with one ovary intact versus, hysterectomy with both ovaries removed versus no hysterectomy [reference group] *) and to determine the association of hysterectomy with ovarian conservation to the development of cardiovascular disease in African-American and white women, adjusting for socio-demographics, lifestyle behaviors (energy intake, physical activity).*

5. Main Hypothesis/Study Questions:

1a. Increasing parity is associated with elevated with Type 2 DM and CRP levels.

1b. After adjustment for life-style risk factors, lipid profiles, and other covariates, parity is positively associated with Type 2 DM.

1c. After adjustment for inflammatory markers (C-reactive protein, sialic acid, orosomucoid, Interleukin-6), the relation of parity with Type 2 DM is attenuated. (Inflammation is a mediator of the relation of parity with Type 2 DM)

2a. Increasing parity is associated with lifestyle risk factors and with the incidence of cardiovascular disease

2b. After adjustment for life-style risk factors, lipid profiles, and other covariates, the relation of parity with cardiovascular disease among African-American and white women is attenuated. (Lifestyle risk factors mediate the relation of parity with cardiovascular disease).

3. Hysterectomy with conservation of one or both ovaries is associated with coronary heart

disease (CHD) after adjustment for socio-demographic and lifestyle risk factors.

6. Data (variables, time window, source, inclusions/exclusions):
Selection data: Women with Type 2 diabetes and women with cardiovascular disease
Exclusions: prevalent type 2 diabetes or prevalent cardiovascular disease at baseline

Primary independent variables:

Reproductive history form: Parity, hysterectomy, removal of one or both ovaries

Dependent variable: incident type 2 diabetes mellitus
Incident cardiovascular disease

Covariates: C-reactive protein, Interleukin-6, sialic acid, orosomucoid levels (from ancillary study by Jim Pankow)
Socio-demographic variables, age, age at hysterectomy, hormone replacement therapy, length of time with HRT, smoking status, HDL- levels, triglycerides, hypertension, sports/leisure/work/physical activity, body mass index, waist circumference, fasting insulin levels

Brief Summary of Statistical Analysis

We will examine the distribution of socio-demographic and clinical characteristics among different categories of parity (0-1, 2-3, 4 or more) using t-tests and chi square statistics. Diabetes incidence rates and incidence of cardiovascular disease will be determined using person-years and compared among parity groups using a test of proportions. The relative risk (RR) of incident diabetes and cardiovascular disease will be determined using proportional hazards models (base model, base model + socio-demographics, base model + socio-demographics + life-style risk behaviors, base model + socio-demographics + life-style risk behaviors+ lipid levels).

In the subanalysis using individual inflammatory markers, we will use statistical methods based on a case-cohort study design with adjustment for sociodemographics, clinical characteristics, and life-style risk factors. Based on the earlier study by Duncan, Pankow et. al, we will conduct a separate analysis using an inflammation index composed of 6 inflammatory markers (Duncan BB et.al, Diabetes, 2003)

7.a. Will the data be used for non-CVD analysis in this manuscript? _x___ Yes ____ 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? __X__ 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

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

In a subgroup of analysis of women with Type 2 diabetes, we propose to adjust for C-reactive protein levels using ancillary data from the case-cohort study by Jim Pankow and colleagues. While Dr. Pankow's studies directly analyses the relation of several inflammatory markers to incident diabetes mellitus, this proposal, in collaboration with Dr. Pankow, will focus on C-reactive protein as a mediator of the relation of parity to incident diabetes mellitus

Dr. Pankow has reviewed this proposal . He and his team have agreed to collaborate on this study and do not believe there is substantial overlap with the ongoing studies of their research team.

11. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

It is expected that manuscript preparation will be completed in two years.

References

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4. Duncan BB, Schmidt M, Pankow JS, Ballantyne CM, Couper D, Vigo A, et. al. Low-Grade Systemic Inflammation and the Development of Type 2 Diabetes. Diabetes 2003;52:1799-1805.

5. Hanley A, McKewon-Evssen G, Harris S, Hegele RA, Wolever T, Kwan J, et. al. Association of Parity with Risk of Type 2 Diabetes and Related Metabolic Disorders. Diabetes Care 2002;25(4):690-695.

6. Pradhan A, Manson J, Rossouw J, Siscovick D, Mouton C, Rifai N, Wallace R, Jackson R, Pettinger M, Ridker P. Inflammatory biomarkders, hormone replacement therapy and incident coronary heart disease. JAMA 2002;288(8):980-987.