Estrogen Exposure, Female Reproductive Factors And Retinal Diseases

Estrogen and Retinal Diseases

Lead: Tien Wong, MD, PhD
Department of Ophthalmology
Centre for Eye Research Australia
University of Melbourne
32 Gisborne Street
Melbourne, VIC 3002
AUSTRALIA
Tel: +61 (3) 99298352 / Fax: +61 (3) 9662 3859, Email: ophwty@nus.edu.sg

Writing group members: Golden S, Magliano D, Klein R, Klein BEK, Hubbard LD, Couper DJ, Sharrett AR

Timeline:
The intent of this analysis is to investigate the cross-sectional association of estrogen/hormone replacement therapy, female reproductive status and retinal diseases (retinal microvascular signs and age-related maculopathy) in women participants of ARIC study. Initial analyses and writing will take place between April and June 2005, and final writing and manuscript submission between July 2005 and Nov 2005.

Rationale:
Estrogen Exposure and Retinal Microvascular Disease
Recent randomized clinical trials have shown that hormone replacement therapy may be associated with an increased risk of cardiovascular disease. However, most studies on the effects of estrogen have focused on large vessel atherosclerotic diseases. There have been considerably fewer studies that have examined possible microvascular changes associated with estrogen use. In experimental studies, estrogen has been linked with microangiopathy in the kidneys of stroke-prone spontaneously hypertensive rats.

An assessment of the calibre of retinal arterioles and venules may provide information regarding the effect of ERT exposure and microvascular disease. Recent analyses in Atherosclerosis Risk in Communities (ARIC) study suggest that narrowed retinal arteriolar diameters are associated with elevated blood pressure, risk of stroke, diabetes, and coronary heart disease. In particular, retinal arteriolar narrowing appeared to predict incident coronary heart disease in middle-aged women but not men, suggesting that microvascular disease may play a more important role in myocardial ischemia in women. The gender difference in risk of heart disease associated with retinal arteriolar narrowing was postulated to be possibly related to microvascular effects of estrogen exposure in women.

Two population-based studies that examined the relationship of ERT, female reproductive factors and retinal vessel diameters provides some evidence to support such a hypothesis. In the Beaver Dam Eye Study, after controlling for age, blood pressure,
body mass index, and cigarette smoking, women who were current users of ERT had significantly narrower retinal arteriolar and venular caliber than those who were past users of ERT and those who had never used ERT, with mean arteriolar diameters of 167.6µm for current, 170.8µm for past and 170.9µm for never users (p=0.009) and mean venular diameters of 239.9µm for current, 244.0µm for past and 243.9µm for never users (p=0.02). In addition, there was a significant trend of increasing narrowing for both arterioles (p trend 0.01) and venules (p trend 0.007) with increasing duration of ERT. Female reproductive factors (e.g., age of menarche and pregnancy) were not associated with retinal vessel diameters.

In the Australian Blue Mountains Eye Study,19 using similar methodology to measure retinal vessel diameters, women who were current users of ERT had significantly narrower arteriolar diameters than women who were never on ERT (odds ratio, 1.4, 95% confidence intervals, 1.0 to 1.9, compared to never users) There were again no relationship between various measures of female reproductive factors and retinal vessel diameter size.

Previous analyses of ERT and female reproductive status in the ARIC study have focused on cardiovascular risk factors and large vessel disease.20,21 In particular, there was no evidence that carotid intima-media thickness was associated with menopausal status, years since menstruation or ERT.21 In the current proposal, we will examine the cross-sectional association of ERT, female reproductive factors and retinal vascular caliber among women participants of the ARIC study.

**Estrogen Exposure and Age-Related Maculopathy**

Age-related maculopathy (ARM) is the leading cause of blindness in elderly people in the United States. Population-based studies suggest that women may have a higher prevalence of ARM.22 It has been hypothesized that estrogen loss due to menopause may be a risk factor for ARM and that ERT may be protective of ARM. However, studies that have examined the relationship between female reproductive factors, ERT and risk of ARM have not found a consistent pattern of associations.23-30

The Eye Disease Case-Control Study first reported a large protective effect of ARM for women who were current (OR = 0.3, 95% CI = 0.1–0.6) or former (OR = 0.6, 95% CI = 0.4–0.9) users of ERT/HRT, and an increased risk was found for women who had one or more children (OR = 1.8, 95% CI = 1.2–2.9).23 Findings from the Rotterdam Study suggested that early menopause due to surgical oophorectomy increased the risk of ARM (OR = 3.8, 95% CI = 1.1–12.6), which could be due to an early decline in estrogen production.27 The Blue Mountains Eye Study reported a significant but modest decrease in the risk of ARM with increasing years from menarche to menopause (OR = 0.97, 95% CI = 0.95–0.99), suggesting that shorter estrogen exposure may be a risk factor for ARM.25 The Beaver Dam Eye Study found that the number of years of ERT/HRT use was inversely associated with all forms of maculopathy, although the relationship only achieved borderline significance (OR = 0.98, 95% CI = 0.96–1.00).26 However, more recent data did not support an association of use of ERT/HRT with incident ARM.28

The current study will provide a further opportunity to explore the association between ERT, female reproductive factors and ARM in middle-aged adults.

5. **Main Hypothesis/Study Questions:**

(1) Is ERT and female reproductive factors associated with retinal vascular diameters?
   - **Hypothesis:** ERT use is associated with narrower retinal arteriolar and venular diameters, independent of blood pressure, markers of inflammation and other factors.

(2) Is ERT and female reproductive factors associated with age-related maculopathy?
Hypothesis: ERT is associated with lower odds of ARM, and early menopause is associated with increased odds of ARM

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

(1) Retinal microvascular variables: Retinopathy, focal arteriolar narrowing, arterio-venous nicking, arteriolar and venular diameters, AV ratio

(2) ARM variables. Any ARM, early ARM, late ARM and specific ARM lesions (drusen, pigmentary changes)

(3) Female reproductive factors. Menopausal status, cause of menopause and HRT use. Definitions, as used by Nebulsi et al20,22 and by Golden et al.31

- Menopausal status: Premenopausal women are those who reported having menstruated in the 2 years before the ARIC visit 3 study examination and who labeled themselves as premenopausal. Perimenopausal women are those who had menstruated in the 2 years before the examination but who label themselves as postmenopausal or as uncertain menopausal status. Women who had not menstruated in the 2 years before the examination were identified as postmenopausal.

- Cause of menopause: Three groups of postmenopausal women are identified according cause of menopause: surgical menopause (bilateral oophorectomy), natural menopause (this group also includes women who had a hysterectomy, at least one intact ovary, and are 55 years of age), and uncertain menopause status (nonmenstruating women with unknown ovarian status, such as those who have a hysterectomy and at least one intact ovary but who are <55 years of age). Three additional groups of postmenopausal women are identified according to the number of years since last menstruation (2 to 5, 6 to 9, or 10 years).

- ERT/HRT status: Postmenopausal women are subclassified into current users of estrogen alone, current users of estrogen plus progestin, former hormone users, and never users. Former users could not be classified accurately by the type of hormone used because of difficulty in recall.

- Endogenous estrogen levels. In a sub-analysis of 362 post-menopausal women who never used HRT, data are available on endogenous estrogen levels (estrone).

(4) Covariates: age, race, center, education, income, occupation, physical activity, prevalent CHD and MI, diabetes and hypertension status, blood pressure, cigarette smoking, alcohol consumption, body mass index, waist hip ratio, hemostatic function indicators (von Willebrand factor, factor VIII, fibrinogen, WBC), variables from ARIC visit 3, except for von Willebrand factor, factor VIII, and WBC, ARIC visit 1 only

(5) Exclusion criteria: From women participants at ARIC visit 3, exclude those whose race is not black/white, with missing/ungradeable retinal photographs, and women with uncertain cause of menopause

Possible Limitations

There are several limitations that need to be addressed. First, there is a possibility of selection bias by health status. For example, women with better health and better access to health care may be more likely to use hormone replacement therapy as well as be less likely to develop retinal disease.

To address this, in the preliminary analyses, we will examine carefully the association between health status variables (i.e. education, income, occupation, physical activity) and retinal variables, and between health status variables and ERT use. This will provide information to understand possible selection biases and potential confounders.
We will also look at relationships with endogenous estrogen, which will further address the limitation of selection. We will examine the associations of endogenous hormone levels with retinal disease and compare this association amongst women who do not use ERT versus those who use ERT.

Finally, we will acknowledge this potential bias in our Discussion, and be conservative in our interpretation of the findings. For example, if we do find a protective effect of ERT for retinal disease, we will discuss all possible reasons for this finding, including selection biases that may be operative.

Second, another possible limitation is the difficulty in determining causal mechanisms related to HRT use in observational studies. Our study is less likely to have bias related to selection of HRT use (“confounding by indication”) since retinal microvascular disease is assessed “subclinically” and persons with (or without) retinal microvascular disease are unlikely to preferentially use (or not use) HRT.

Finally, a third possible limitation is misclassification of menopausal status. To address, we will perform sensitivity sub-analyses by (a) excluding women who are classified as “perimenopausal” and (b) re-classifying perimenopausal women as either “post” or “pre-menopausal”.

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 ICTDER01 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 ICTDER01 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 ICTDER01 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/csec/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)?

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ___ Yes _X_ No

11.b. If yes, is the proposal ___ A. primarily the result of an ancillary study (list number* _________)
B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s))* __________ __________ __________

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. 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.

References
17. Maguire MG. Explaining Gender Differences in Coronary Heart Disease: Hunting for Clues With the Ophthalmoscope. Arch Ophthalmology 2003;121:1328-1329