Female Reproductive Factors and Eye Disease in a Rural South Indian Population: The Aravind Comprehensive Eye Survey

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PURPOSE. To determine the potential associations of female reproductive factors with age-related cataract, open-angle glaucoma, macular degeneration, and myopia in an older population of rural south India.

METHODS. This was a population-based, cross-sectional study of older adults in rural south India identified through a cluster sampling technique. Histories relating to female reproductive factors were ascertained through a questionnaire administered by trained workers. Detailed ocular examinations including automated perimetry were performed on all participants at a base hospital to arrive at a diagnosis of ocular morbidity.

RESULTS. The study achieved a high response rate (93.0%), with examinations performed on 5150 of the eligible 5559 persons aged 40 years or more. Age at menarche was available for 2797 (98.6%) of the women and age at natural menopause for 1841 (98.0%) of 1878 women who were postmenopausal. The mean age at menarche was 14.8 ± 1.8 years, and the mean age at menopause was 45.4 ± 3.9 years. The mean duration of endogenous estrogen exposure was 28.4 ± 4.3 years. The median number of pregnancies was 4 (mean, 4.3 ± 2.6; range, 0–16). Older age at menarche (≥14 years) was associated with reduced risk for age-related cataract and myopia, and greater risk for macular degeneration. Neither age at menopause nor duration of endogenous estrogen exposure was associated with any of the ocular diseases studied. Parity was not associated with any of the ocular diseases studied in a multivariate model.

CONCLUSIONS. Female reproductive factors do not appear to influence age-related cataract, open-angle glaucoma, macular degeneration or myopia significantly in rural south India. (Invest Ophthalmol Vis Sci. 2004;45:4273–4276) DOI:10.1167/iovs.04-0285

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Supported in part by unrestricted grants from Allergan, Inc., Alcon Laboratories, Inc., and Carl Zeiss Meditec, and Aravind Medical Research Foundation.

Submitted for publication March 12, 2004; revised August 8, 2004; accepted August 25, 2004.

Disclosure: P.K. Nirmalan, None; J. Katz, None; A.L. Robin, None; R. Ramakrishnan, None; R. Krishnadas, None; R.D. Thulasiraj, None; J.M. Tielsch, None

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A ge-related cataracts, open-angle glaucoma, macular degeneration, and myopia are major causes of vision impairment and blindness worldwide.1 The potential influence of female hormones on eye diseases, especially age-related cataract, diabetic retinopathy, age-related maculopathy, and dry eye, have been explored in developed countries where postmenopausal hormone replacement therapy has been relatively common.2–8 Both the Blue Mountains and the Rotterdam studies have reported reduced odds for open-angle glaucoma in hormone replacement users although the strength of evidence for this protective effect was weak, with neither of the associations reaching statistical significance.9,10 As part of a comprehensive eye disease prevalence survey, we decided to examine the potential influence of female reproductive history on the major ocular diseases of adults in a rural population in south India, where access to hormone replacement therapy is very limited.

METHODS

The Aravind Comprehensive Eye Survey (ACES) is a population-based, cross-sectional study exploring the burden of visual impairment and blindness in a rural population aged 40 years and older in three districts of southern India. The study design and methodology have been described in detail elsewhere.11 Briefly, we identified the study population from the Madurai, Tirunelveli, and Tuticorin districts of southern India through a stratified systematic random cluster sampling technique. We offered comprehensive eye examinations to subjects who were identified as eligible for inclusion in the study. The comprehensive ocular examinations were performed at the base hospitals by examiners who were standardized to each other. The examinations included slit lamp biomicroscopy, lens grading according to the Lens Opacification Classification System (LOCS) III,12 applanation tonometry, gonioscopy, visual fields assessed by automated perimetry, and dilated fundus examinations with indirect ophthalmoscopy and 90-D lens in all subjects. Visual acuity was measured with Early Treatment Diabetic Retinopathy Study (ETDRS) charts, and refraction was performed in all subjects. The examiners were standardized before the start of the study and at regular intervals during the study period.

We defined a definite cataract as LOCS III nuclear opalescence ≥ 3.0 and/or cortical cataract ≥ 3.0 and/or posterior subcapsular cataract (PSC) ≥ 2.0. We defined definite primary open-angle glaucoma (POAG) as angles open on gonioscopy, and glaucomatous optic disc changes with matching visual field defects.13 The diagnosis of glaucoma was made independent of intraocular pressure and was based on stereoscopic optic nerve appearance and perimetry. When analyzing intracranial pressures, we considered the higher median pressure of the two eyes. We defined age-related maculopathy (ARM) according to the international classification developed by the International ARM Epimediologic Study Group.14 Briefly, we defined drusen as discrete whitish-yellow spots external to the neuroretinal or the retinal pigment epithelium (RPE). Pigmentary abnormalities included either increased pigmentation associated with drusen or depigmentation or hypopigmentation of the RPE, more sharply demarcated than drusen, without any visibility of choroidal vessels associated with drusen. Geographical atrophy was defined as any sharply delineated, roughly round or oval
area of hypopigmentation or depigmentation or apparent absence of the RPE in which choroidal vessels were more visible than in the surrounding areas, at least 175 μm in size. Exudative AMD was defined as the presence of any of the following: RPE detachments or serous detachment of the sensory retina; subretinal or sub-RPE neovascular membrane; subretinal hemorrhage; and epiretinal, subretinal, intraretinal, or subpigment epithelial scarring or glial tissue or fibrin-like deposits. Early ARM was defined as the presence of soft, large drusen (>125 μm) with pigment epithelial abnormalities. Late ARM was defined as the presence of signs of exudative age-related macular degeneration or geographic atrophy. We defined myopia as a spherical equivalent refraction worse than 1.00 D. The presence of pseudoexfoliation on the lens, pupillary margins, cornea, vitreous face, and angles was looked for and recorded.

Before the ocular examinations, trained field workers conducted interviews with a structured questionnaire; to collect demographic and other details. We specifically sought details relating to reproductive factors including ages at menarche and menopause and the number of pregnancies and children. We did not ask about details of hormone replacement therapy, use of oral contraceptives, and hysterectomy, as hormone replacement therapy and hysterectomy are almost nonexistent practices in this older rural population. Age at menopause was defined as the age at natural menopause. We calculated duration of endogenous estrogen exposure as the number of years between reported age at menarche and age at menopause, if the woman was postmenopausal, and as the difference between age at menarche and current age, if the woman was premenopausal.

We measured the blood pressure of each study participant after subjects had rested at least 5 minutes in a seated position. We defined systemic hypertension as either a measured systolic blood pressure of >160 mm Hg and/or a diastolic blood pressure of >95 mm Hg or current use of systemic antihypertensive medications. We used a glau- meter and strips to test for blood sugar levels. We obtained capillary blood samples by pricking the finger with a sterile lancet 2 hours after the subject had breakfast. We defined diabetes as a measured postprandial blood sugar of ≥180 mg/dL or current use of blood-sugar-lowering medications. We did not perform measurement of glycosylated hemoglobin, because facilities for this test were not available in the study districts during the study period.

The study protocol was approved by the Institutional Review Board/Committee, Aravind Eye Hospital, Madurai, and the Committee on Human Research at the Johns Hopkins Bloomberg School of Public Health. Informed consent was obtained at three different levels before the actual study: community, household, and individual. Meetings were held with community leaders and all health-related personel in the area to explain the purpose of the study. On occasion approval was obtained at these meetings, the study was fully explained to all adults in the household to address any concerns and to secure consent for members of the household to participate. Before both screening and definitive examinations, the study was explained in detail to all potential participants, and their voluntary consent was solicited. All informed consent was verbally obtained, because a significant proportion of this population is illiterate. The study abided by the tenets of the Declaration of Helsinki.

A computer software (STATA, ver. 7.0; Stata Corp., College Station, TX) was used for statistical analyses. We performed bivariate and multivariate logistic regression exploring for associations of diseases with endogenous estrogen exposure, age at menarche, and parity. We considered variables that were significant on bivariate analysis for inclusion in the multivariate models. For instance, macular degeneration was associated only with age on bivariate analyses; hence, we included only age in the multivariate analyses for parity and macular degeneration. We did not seek any associations between parity and myopia, since myopia generally develops at ages before pregnancy. We explored interactions between variables in the multiple logistic models by adding interaction terms to the regression models as required. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. We considered P < 0.05 to denote statistical significance for the analysis.

**RESULTS**

A high response rate (93.0%) was achieved in ACES with 5150 of the eligible 5539 persons aged 40 years or more examined, and 2836 (55.0%) women were included. The median age of the women in the study was 50.0 years (mean, 51.3 ± 9.5 years; range, 40–85 years). Nine hundred fifty-eight (38.8%) women were still menstruating at the time of the study. Age at menarche was available for 2797 (98.6%) of women, and age at natural menopause for 1841 (98.0%) of 1878 women who were postmenopausal. The mean age at menarche was 14.8 ± 1.8 years and the mean age at menopause was 43.4 ± 3.9 years. The median reported age at menarche or at menopause did not differ by age group. The mean duration of endogenous estrogen exposure was 28.4 ± 4.3 years. The median number of pregnancies was 4 (mean, 4.3 ± 2.6; range, 0–16).

Open-angle glaucoma was found in 20 (0.7%) of the participants, definite cataract in 1314 (46.3%; 95% CI: 42.3–50.3; design effect, 1.3), and macular degeneration, either early or late, in 86 (3.2%), with prevalence of all three disorders increasing with age. The majority of the women (n = 2820, 99.4%) had never smoked any tobacco products.

There was no association between open-angle glaucoma and age at menarche, age at menopause, or duration of endogenous estrogen exposure (Table 1). On bivariate analysis, age at menarche of ≥14 years, age at menopause ≤45 years or younger, and endogenous estrogen exposure for <30 years was associated with presence of any cataract. However, on multivariate analysis after adjusting for age, diabetes, body mass indices, and pseudoexfoliation, only age at menarche remained significantly associated with any cataract, with older age at menarche (>14 years of age) showing a protective effect. Lower duration of endogenous estrogen exposure (<35 years) and later age at menarche was associated with macular degeneration on bivariate analysis. However, only age at menarche was significant in a multivariate regression analysis that included age. Females who were aged 14 years or older at menarche had a higher odds of macular degeneration (Table 1). Menarche earlier than 14 years of age was associated with myopia in bivariate and multivariate analysis. Although endog- enous estrogen exposure <30 years was associated with myopia on bivariate analysis, the association was no longer significant on multivariate analysis.

We further explored the association of cataract phenotypes with female reproductive factors after adjusting for age, diabe- tes, pseudoexfoliation, and body mass index. Older age at menarche was protective for nuclear cataract (OR: 0.6; 95% CI: 0.5–0.8) and PSC (OR: 0.8; 95% CI: 0.6–1.0). Younger age at menopause was associated with nuclear cataract (test score for trend of odds: 17.9, P < 0.01) and PSC (test score for trend of odds: 10.2, P = 0.001). Shorter duration of endogenous estrogen exposure was associated only with nuclear cataract (test score for trend of odds: 15.0, P = 0.0001). Cortical cataracts did not show any association with age at menarche or meno-pause or duration of endogenous estrogen exposure.

Open-angle glaucoma, age-related cataracts (any cataract and individual phenotypes), or macular degeneration were not associated with parity on bivariate or multivariate analysis after adjusting for age and other risk factors for these diseases (Table 2).

**DISCUSSION**

The high response rates to interviews and ocular examination (93.0%) after door-to-door enumeration of a randomly chosen sample, the large sample size, and the lack of exogenous estrogen supplementation in this population are major strengths of our study. However, there are several limitations.
Table 1. OR and 95% CI for Associations Between Female Reproductive Factors and Eye Disease

<table>
<thead>
<tr>
<th>Factors</th>
<th>Number at Risk (%)</th>
<th>Case (%)</th>
<th>Multivariate Adjusted</th>
<th>OAG</th>
<th>Cataract</th>
<th>Macular Degeneration</th>
<th>Myopia</th>
<th>Multivariate Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at menarche</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥13 years</td>
<td>662 (23.7)</td>
<td>5 (0.8)</td>
<td>1.0</td>
<td>332 (50.2)</td>
<td>1.0</td>
<td>10 (1.5)</td>
<td>1.0</td>
<td>257 (38.8)</td>
</tr>
<tr>
<td>14+</td>
<td>2135 (76.3)</td>
<td>15 (0.7)</td>
<td>1.0 (0.3–2.9)</td>
<td>955 (44.7)</td>
<td>0.7 (0.5–0.9)</td>
<td>76 (3.7)</td>
<td>2.3 (1.2–4.7)</td>
<td>726 (34.0)</td>
</tr>
<tr>
<td>Age at menopause</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 years</td>
<td>125 (4.5)</td>
<td>1 (0.8)</td>
<td>1.0</td>
<td>75 (60.0)</td>
<td>1.0</td>
<td>2 (1.7)</td>
<td>1.0</td>
<td>54 (43.2)</td>
</tr>
<tr>
<td>&lt;50 years</td>
<td>603 (21.5)</td>
<td>8 (1.3)</td>
<td>1.1 (0.9–14.5)</td>
<td>395 (65.5)</td>
<td>1.5 (0.8–2.6)</td>
<td>38 (6.8)</td>
<td>2.3 (0.5–12.3)</td>
<td>285 (47.3)</td>
</tr>
<tr>
<td>Endogenous estrogen exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥35 years</td>
<td>187 (6.7)</td>
<td>1 (0.5)</td>
<td>1.0</td>
<td>111 (59.4)</td>
<td>1.0</td>
<td>2 (1.1)</td>
<td>1.0</td>
<td>74 (39.6)</td>
</tr>
<tr>
<td>30–34 years</td>
<td>876 (31.3)</td>
<td>10 (1.1)</td>
<td>2.2 (0.2–27.1)</td>
<td>484 (55.2)</td>
<td>1.1 (0.7–1.8)</td>
<td>40 (4.9)</td>
<td>2.7 (0.5–13.9)</td>
<td>360 (41.1)</td>
</tr>
<tr>
<td>&lt;30 years</td>
<td>1734 (62.0)</td>
<td>9 (0.5)</td>
<td>1.6 (0.1–25.0)</td>
<td>692 (39.9)</td>
<td>1.2 (0.7–1.9)</td>
<td>44 (2.6)</td>
<td>2.2 (0.4–12.0)</td>
<td>549 (31.7)</td>
</tr>
</tbody>
</table>

Multivariate models for open-angle glaucoma were adjusted for age; diabetes, pseudoexfoliation, and myopia. For cataract, the model was adjusted for age, pseudoexfoliation, diabetes, and body mass indices. For both macular degeneration and myopia, the models were adjusted for age. OAG, open-angle glaucoma.

* P < 0.05.

Table 2. OR and 95% CI for Associations between Parity and Eye Diseases

<table>
<thead>
<tr>
<th>Factors</th>
<th>Number at Risk (%)</th>
<th>Case (%)</th>
<th>Age Adjusted</th>
<th>Multivariate Adjusted</th>
<th>OAG</th>
<th>Cataract</th>
<th>Macular Degeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity (0)</td>
<td>167 (5.9)</td>
<td>1 (0.6)</td>
<td>1.0</td>
<td>1.0</td>
<td>89 (53.3)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1–2</td>
<td>519 (18.3)</td>
<td>0 (0.0)</td>
<td>—</td>
<td>—</td>
<td>233 (44.9)</td>
<td>0.8 (0.5–1.3)</td>
<td>1.0 (0.6–1.6)</td>
</tr>
<tr>
<td>3–4</td>
<td>896 (31.6)</td>
<td>5 (0.6)</td>
<td>1.3 (0.2–9.6)</td>
<td>1.3 (0.2–11.5)</td>
<td>339 (37.8)</td>
<td>0.7 (0.4–1.1)</td>
<td>0.8 (0.5–1.2)</td>
</tr>
<tr>
<td>≥5</td>
<td>1253 (44.2)</td>
<td>14 (1.1)</td>
<td>1.5 (0.2–12.0)</td>
<td>1.7 (0.2–13.4)</td>
<td>652 (52.0)</td>
<td>0.7 (0.5–1.1)</td>
<td>0.8 (0.5–1.3)</td>
</tr>
</tbody>
</table>

Multivariate model adjustments are described in Table 1. OAG, open-angle glaucoma.

to be considered when interpreting our findings. A major limitation is the potential for recall error associated with self-reported ages at menarche and menopause that can impact determination of the duration of endogenous estrogen exposure. Menarche is traditionally celebrated in these rural populations and is less likely to be subject to recall error. Determination of an accurate age at menopause is potentially problematic. Any irregular pattern of menstruation may cause difficulties in elucidating an accurate age at menopause, and there is a possibility that we may have misclassified women who were perimenopausal. Estimations of duration of endogenous estrogen exposure may also be influenced by periods of amenorrhea, for which no data were collected during our survey. However, these problems of accurately defining menopause and duration of endogenous production are not limited to our specific population. As we have reported, most of the subjects with glaucoma and other eye diseases had not had eye disease diagnosed before our study, minimizing the potential for any differential recall between cases and controls. It is not clear how any potential misclassifications may have impacted our results, although the potential nondifferential misclassification may underestimate the true risk of the disease associated with the exposure. We could not collect information on socioeconomic status (SES) across a lifespan, since our data collection was cross-sectional in nature, and hence we were unable to explore potential any confounding between SES and either age at menarche or menopause. We are also unable to comment on the impact of differential mortality, if any, on our results.

Our findings do not support an association of female reproductive factors and open-angle glaucoma, although with only 20 cases, the ability to look at this issue was limited. Similar to a recent report from the Blue Mountains Study,10 we found increased odds for open-angle glaucoma among women reporting early natural menopause and shorter duration of endogenous estrogen exposure, although these were not statistically significant in a multivariate model. An increased odds ratio, although not at statistically significant levels for increasing parity with open-angle glaucoma, is also similar to that reported from the Blue Mountains Study.10 Our population, was however, much younger (mean age, 51.3 years) than the population in the Blue Mountains Study10 (mean age, 66.8 years) or the Rotterdam study10 (mean age, 68.8 years), which reported associations of open-angle glaucoma and female reproductive factors. The reported mean age at menopause was also lower in our population (43.4 years) than in the Blue Mountains Study10 (47.8 years) and the Rotterdam (48.8 years) study populations. Further longitudinal follow-up of these subjects may reveal protective or deleterious effects, especially if such effects are mild to moderate.

We found older age at menarche to be protective against age-related cataract, macular degeneration, and myopia. The protective effect (of borderline statistical significance) of older age at menarche against age-related cataract is in contrast to reports from the Beaver Dam Eye Study, which reported increasing severity of nuclear sclerosis to be associated with older age at menarche.4 The differences between the two studies may differ the definitions of the end point of lens...
opacities and differences in age distribution, environmental exposure, or genetic factors. The Beaver Dam Eye Study also reported no association of female reproductive factors with ARM.5 Our study had very few cases of late maculopathy and so had limited statistical power to address this question. Longitudinal studies may be needed to test any hypothesis relating to protective or deleterious effects of female reproductive factors and age related maculopathy.

References