

SCIENTIFIC REPORT

Female reproductive factors and open angle glaucoma: the Blue Mountains Eye Study

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Aims: To determine whether endogenous oestrogen exposures are associated with open angle glaucoma (OAG).

Methods: The Blue Mountains Eye Study examined 2072 women aged 49–97 years during 1992–4. Questions about female reproductive factors included age at menarche and menopause, parity, and use of hormone replacement therapy. Applanation tonometry, visual field tests, and stereo-optic disc photographs were performed. OAG was diagnosed when glaucomatous visual fields matched optic disc changes. Ocular hypertension (OH) was defined in the absence of glaucoma, but with intraocular pressure ≥ 22 mm Hg.

Results: A significantly increased OAG risk with later (>13 years) compared with earlier (≤ 12 years) age of menarche was found, odds ratio (OR)=2.0; 95% confidence interval (CI) 1.0 to 3.9, p for trend=0.01, after adjustment for multiple confounders. Non-significant increased odds for OAG were found for early natural menopause (<45 years) compared with the reference group (≥ 50 years), adjusted OR=1.7; CI: 0.7 to 3.8, and for shorter duration of endogenous oestrogen exposure (<30 years), adjusted OR=1.8; CI: 0.6 to 5.3. Increasing parity was associated with an increased risk of OAG ($p=0.03$) and decreased risk of OH ($p=0.03$).

Conclusion: The modest associations found in relation to late menarche and increased parity do not allow the exclusion of a possible role for endogenous female hormones in the pathogenesis of OAG.

Open angle glaucoma (OAG) is a leading cause of bilateral blindness worldwide.¹ A male bias has been documented in some^{2,3} but not in all^{4,5} glaucoma prevalence reports, thus alluding to a possible protective role of female sex hormones in OAG pathogenesis. Coupled with controversy over use of hormone replacement therapy⁶ with respect to the relative cardiovascular⁷ and skeletal benefits⁸ opposing the risk of endometrial⁹ and breast carcinoma,¹⁰ the evaluation of female sex hormone influence on eye disease is of particular interest.

To date, the role of female hormones in relation to cataract,^{11–14} age related maculopathy,^{14,15} diabetic retinopathy,¹⁶ and dry eye syndrome¹⁷ has been studied. Recently, the Rotterdam study reported a significantly reduced OAG risk in women associated with longer duration of endogenous oestrogen exposure.¹⁸

From the Blue Mountains Eye Study we aimed to test the hypothesis that shorter endogenous oestrogen exposure is related to OAG prevalence. This also provided an opportunity to assess whether OAG was associated with other reproductive parameters, the use of hormone replacement therapy, or the oral contraceptive pill.

PATIENTS AND METHODS

The Blue Mountains Eye Study (BMES) surveyed common eye diseases in permanent residents aged 49+ years, living in the Blue Mountains region, west of Sydney, Australia, during 1992–4. Previous reports have described this study.^{5,12} Of 2498 eligible female residents, 2072 (82.9%) took part in the study. Most participants were white. The western Sydney area human ethics committee approved this project and written informed consent was obtained from all participants.

Study participants underwent standardised subjective refraction, applanation tonometry, Humphrey suprathreshold perimetry (Allergan Humphrey, San Leandro, CA, USA), and Zeiss stereoscopic 30° colour optic disc photography (Carl Zeiss, Oberkochen, Germany). Subjects with a history of glaucoma or glaucomatous visual field or optic disc features, were invited for 30-2 full threshold tests (completed by 9.2% of subjects). Masked grading of photographs followed established protocols.⁵

OAG was diagnosed⁵ when typical glaucomatous visual field loss matched optic disc cupping and rim thinning (cup-disc ratio ≥ 0.7 or cup-disc asymmetry ≥ 0.3) with normal gonioscopy. Elevated intraocular pressure (IOP) was not included as a criterion for OAG diagnosis. Ocular hypertension (OH) was diagnosed in subjects with IOP ≥ 22 mm Hg but without glaucomatous disc or field changes. Myopia was defined in eyes with spherical equivalent refraction ≥ -1.00 dioptres. IOP analyses used the maximum IOP of the two eyes, and excluded subjects taking glaucoma medications.

Trained interviewers asked women questions about reproductive factors including ages when menstrual periods started (menarche) and ended (menopause); number of pregnancies and children; type of menopause; history of hysterectomy with or without oophorectomy; use of oral contraception; and ever use of hormone replacement therapy.

Natural menopause included women who did not cease menstruating because of a hysterectomy and surgical menopause included those women who had a hysterectomy. Duration of endogenous oestrogen exposure was taken as the number of years between reported age at menarche and menopause. Analyses regarding age at menopause and duration of endogenous oestrogen exposure were subdivided into two categories; all postmenopausal women, and those reporting natural menopause. Both these categories excluded women with a history of premenopausal hysterectomy without oophorectomy ($n=255$) as age at hysterectomy in these women would underestimate age at menopause.¹¹ If data were missing for menopausal status and age at examination was above 65 years, participants were considered post-menopausal. Women using hormone patches (but not creams) were included in analyses. Women who had ever used hormone replacement but could not recall the preparation type ($n=271$), were included in analyses of ever users. No data on type or duration of use were collected for past use of hormone preparations.

History of hypertension, diabetes, and glaucoma family history were also collected. Seated blood pressure was measured in each subject and fasting venous blood glucose was taken in 88% of returning participants. Systemic hypertension was defined as a history of high blood pressure (BP), current use of antihypertensive treatment and/or systolic BP >160 mm Hg and/or diastolic BP >95 mm Hg. Diabetes was defined from history or fasting venous glucose ≥ 7.8 mmol/l.

All statistical analyses, including χ^2 , Mantel-Haenszel test, and logistic regression were performed using Statistical Analysis System (SAS Institute, Inc, Cary, NY, USA). In multivariate logistic regression, adjustment for potential confounders including age, diabetes, hypertension, myopia, pseudoexfoliation and glaucoma family history, were performed.

We categorised ages at menarche and menopause, duration of exposure to endogenous oestrogen and parity as shown. We tested for trends in duration by modelling the median duration (years) in each category as a single continuous variable. Interactions between exposure variable and age and type of menopause were assessed by using the Breslow-Day test for heterogeneity in stratified analyses and adding interaction terms to cumulative odds models. Odds ratios (OR) and 95% confidence intervals (CI) are presented. p Values <0.05 were considered statistically significant.

RESULTS

Of 2498 eligible females, 2072 (82.9%) participated. The median age was 65 years, mean age 66.4, and range 49–97 years. The age and sex characteristics of OAG and OH cases are described elsewhere.⁵ In brief, OAG was diagnosed in 72

women (3.5%) and OH in 105 women (5.3%). OAG prevalence increased exponentially with age.⁵ A borderline increased odds for OAG in women was found (age adjusted OR = 1.55; CI: 1.0 to 2.3).

Menstrual status was documented in 2032 women (98.1%); 79 subjects (3.9%) were still menstruating and 1953 (96.1%) had stopped. Type of menopause was recorded in 1814 women; 1276 (70.3%) had a natural menopause and 538 (29.7%) a surgical menopause, including 185 with history of having had both a hysterectomy and oophorectomy, 260 who had hysterectomy only and 93 women who were not sure whether their ovaries had been removed. Women who underwent surgical menopause were younger at menopause (41.8 years) than those reporting natural menopause (49.1 years).

The mean age at menarche was 13.2 years and mean age at menopause was 47.8 years. Women aged 80+ years reported menarche at an older age (median age of menarche = 14 years) than those aged <60 (median age of menarche = 13). The median age of menopause for each 10 year age group was similar. The mean duration of endogenous oestrogen exposure was 34.6 years. Median parity was two children (range 0–10).

Use of hormone replacement therapy was reported by 557 women (26.9%); 324 were current and 233 past users. The mean age of current users (60 years) was younger than both past (64.4 years) and never users (68.7 years). Use of oral contraception was reported by 649 women (31.3%), with younger mean age (59 years) than never users (69 years). Data regarding ever use of hormone replacement therapy were missing for 198 women; and ever use of the oral contraceptive pill for 112 women.

Table 1 Odds ratios (OR) and 95% confidence intervals (CI) for associations between open angle glaucoma and reproductive factors

Characteristic	OR and 95% CI			
	Glaucoma		Age adjusted	Multivariate adjusted*
	No at risk	%		
Age at menarche (years)				
<13	691	2.0	1.0	1.0
13	441	2.3	2.0 (1.1 to 3.7)	2.1 (1.1 to 3.8)
14+	824	5.0	1.9 (1.0 to 3.6)	2.0 (1.0 to 3.9)
			p for trend=0.01	p for trend=0.01
Age at menopause† (years)				
All post-menopausal women				
50+	788	3.3	1.0	1.0
45–49	442	3.9	1.3 (0.7 to 2.4)	1.2 (0.6 to 2.3)
<45	340	4.7	1.4 (0.7 to 2.8)	1.3 (0.7 to 2.6)
			p for trend=0.26	p for trend=0.40
Natural menopause‡				
50+	719	3.1	1.0	1.0
45–49	346	3.8	1.3 (0.6–2.6)	1.2 (0.6–2.5)
<45	164	6.1	1.8 (0.8–4.0)	1.7 (0.7–3.8)
			p for trend=0.14	p for trend=0.24
Duration of endogenous oestrogen exposure† (years)				
All post-menopausal women				
40+	297	2.4	1.0	1.0
35–39	629	3.5	1.4 (0.6 to 3.4)	1.4 (0.6 to 3.3)
30–34	346	4.9	1.9 (0.8 to 4.7)	1.7 (0.7 to 4.3)
<30	287	4.5	1.8 (0.7 to 4.6)	1.6 (0.6 to 4.3)
			p for trend=0.19	p for trend=0.29
Natural menopause‡				
40+	266	2.6	1.0	1.0
35–39	550	2.7	1.0 (0.4 to 2.5)	0.9 (0.4 to 2.4)
30–34	270	5.6	1.8 (0.7 to 4.7)	1.6 (0.6 to 4.2)
<30	133	6.0	1.8 (0.6 to 5.4)	1.8 (0.6 to 5.3)
			p for trend=0.09	p for trend=0.14

*Adjusted for age, history of diabetes, hypertension, myopia, pseudoexfoliation, and family history of glaucoma.

†Excludes women with a hysterectomy only (n=255). ‡Age at natural menopause missing in 47 women.

Table 2 Odds ratios (OR) and 95% confidence intervals (CI) for associations between parity and open angle glaucoma and ocular hypertension

OR and 95% CI		Ocular hypertension			
Glaucoma		No at risk	%	Age adjusted	Multivariate adjusted*
Parity					
0	400	385	6.0	1.0	1.0
1-2	746	725	6.6	1.1 (0.7 to 1.9)	1.1 (0.7 to 1.9)
3-4	643	618	4.9	0.8 (0.5 to 1.4)	0.8 (0.5 to 1.4)
≥5	193	179	1.1	0.2 (0.04 to 0.8)	0.2 (0.04 to 0.8)
				p for trend = 0.03	p for trend = 0.03

*Adjusted for age, history of diabetes, hypertension, myopia, pseudoexfoliation, and family history of glaucoma.

Table 1 shows the relation between OAG and age at menarche, age at menopause, and duration of endogenous oestrogen exposure. Statistically significant trends, with twofold increased odds, were found between OAG and later menarche, after multivariate adjustment, p , trend = 0.01.

Among post-menopausal women, increased age adjusted odds for the association between OAG and earlier age at menopause (<45 years) were observed. For women reporting a natural menopause, even higher odds were found, though this remained non-significant (OR = 1.8; CI: 0.8 to 4.0). Analysis of the duration of endogenous oestrogen exposure among women reporting a natural menopause suggested that shorter duration may be associated with increased OAG risk (age adjusted p for trend = 0.09). Different types of menopause (natural *v* surgical) were not associated with OAG. These findings did not alter appreciably when use of hormone replacement was included in analyses.

Parity was positively correlated with OAG, p (trend) = 0.03, but negatively with OH, p (trend) = 0.03, shown in Table 2. Women with at least five children had a more than twofold increased risk of OAG (multivariate adjusted OR = 2.5; CI: 1.0 to 6.1) but lower risk of OH (multivariate adjusted OR = 0.2; CI: 0.04 to 0.8).

Associations between OAG and use of either hormone replacement therapy or oral contraception are shown in Table 3. Lower OAG odds were found in women reporting past use of hormone replacement therapy (multivariate adjusted OR = 0.3; CI: 0. to -1.1) and ever use of oral contraception, multivariate adjusted OR = 0.4; CI: 0.2 to 1.2, but neither was statistically significant. When we examined maximum IOP of the two eyes (similar results found for average IOP), women reporting current use of hormone replacement had slightly lower IOP than past or never users (age adjusted p = 0.03), as shown in Table 4. After stratifying by ever use of hormone replacement, mean IOP was 0.6 mm Hg lower in current than in past users (p = 0.02, multivariate adjusted). No IOP associations were found in relation to menstrual status or age at menopause.

No significant trends were found for the relation between OH and older age at menarche, younger age at menopause, or shorter duration of endogenous oestrogen exposure. There were no associations between OH and use of either hormone replacement or oral contraceptives.

DISCUSSION

Our findings provide only limited support for the recent Rotterdam Study hypothesis¹⁸ that early menopause may be an OAG risk factor in women. Our data support the possibility that OAG may be more frequent among women with shorter endogenous hormone exposures. We found significantly increased odds for OAG in women reporting later age at menarche. However, although we documented increased odds for OAG among women reporting early natural menopause and shorter duration of endogenous oestrogen exposure, neither was statistically significant in our model that included age and other OAG risk factors. Our findings of higher OAG prevalence in women reporting higher parity also suggests a role of reproductive factors in OAG pathogenesis.

Our findings have important limitations; the study was based on self reported ages at menarche and menopause, so recall bias could be important. This is not likely to have been affected by presence of glaucoma.¹⁸ Women at the perimenopausal stage may have been misclassified as age at menopause based on the last menstrual period and can only be determined retrospectively. Our measures of endogenous oestrogen exposure were fairly crude and the durations calculated do not account for periods of amenorrhoea. Serum or urine sex hormone levels were not measured. Small

Table 3 Odds ratios (OR) and 95% confidence intervals (CI) for associations between open angle glaucoma and use of hormone replacement therapy or the oral contraceptive pill

Characteristic	Odds ratios and 95% CI			
	Glaucoma		Age adjusted	Multivariate adjusted*
	No at risk	%		
Hormone replacement therapy				
Never	1317	4.5	1.0	1.0
Ever	557	1.3	0.5 (0.2 to 1.2)	0.5 (0.2 to 1.2)
Current users	324	1.5	0.8 (0.3 to 2.0)	0.8 (0.3 to 2.2)
Past users	233	0.9	0.3 (0.1 to 1.2)	0.3 (0.1 to 1.1)
Oral contraceptive use				
Never users	1311	4.6	1.0	1.0
Ever users	649	0.8	0.5 (0.2 to 1.2)	0.4 (0.2 to 1.2)

*Adjusted for age, history of diabetes, hypertension, myopia, pseudoexfoliation, and family history of glaucoma.

numbers in many subcategories may have limited evaluation of some associations. Factors affecting hormone replacement use such as education, alcohol consumption, and smoking were not adjusted for owing to loss of power.

The strengths of our study include its defined population base, relatively large sample size, and high participation rate. OAG signs were carefully determined and the diagnosis independently adjudicated. We excluded women who reported only a hysterectomy from analyses of the age at menopause and duration of endogenous oestrogen exposure, as continued ovarian follicular function would preclude accurate determination of menopause.¹⁹ Using logistic regression models, we controlled for multiple potential confounders for OAG and IOP.

Despite finding increased odds for the association between OAG and earlier age of natural menopause, we could not confirm the significant relation reported by the Rotterdam Study.¹⁸ Although our methodology was similar, the mean ages of our group (66.8 v 68.8 years) and age at menopause (47.8 v 48.8 years) were younger, which could have led to an underestimate of its effect in our population. OAG was related to later age at menarche (≥ 13 years) in our data, suggesting influences either from shorter endogenous oestrogen exposure or from pubertal hormonal changes on OAG pathogenesis. Previous studies include a finding that earlier age at menarche is associated with lower prevalence of cataract types,¹² nuclear cataract,²⁰ and incidence of cataract surgery.¹¹

The Rotterdam study proposed that age at natural menopause is a surrogate for endogenous oestrogen exposure. Age at menarche could be considered a similar proxy; recall of age at menarche, a once only milestone in a woman's life, may possibly be more accurate than recall of the age at

natural menopause, characterised by an irregular pattern of menstruation before the final period.²¹ Furthermore, a definitive diagnosis of menopause can only be made 12 months after the last menstrual period.¹⁹ It has been suggested that hormonal activity in youth would have a lesser effect on the risk of glaucoma than cessation of hormonal activity during middle age.¹⁸ However, rapid elevation of oestradiol levels during puberty has been considered to have a greater impact on disease than the gradual decline during the climacteric period.²¹

Recent experimental evidence supports a protective role for female sex hormones, particularly oestrogen, in OAG development. Oestrogen receptors have been localised in neural retinas of animal²² and human eyes.²³ After receptor activation, enhanced activity of endothelial based type-3 nitric oxide synthase²⁴ occurs with resultant local release of vasodilatory nitric oxide.²⁵ Reduced vascular resistance associated with oestrogen use has also been documented.²⁵ In view of the proposed pathogenetic role of ocular ischaemia and increased vascular resistance in OAG,²⁶ these features are of particular interest. Nitric oxide modulated IOP reduction via changes in aqueous outflow resistance in the trabecular meshwork has also been postulated.²⁷⁻²⁸

Neuroprotection by oestrogen has also been proposed.²²⁻²⁹ Together with the premise that glaucoma is a neurodegenerative disease,¹⁸⁻³⁰⁻³¹ a possible preventive role for oestrogen in the irreversible loss of retinal ganglion cells either directly³² or by vascular mechanisms, is plausible.

In light of observed improved OAG control during pregnancy,³³ the relation demonstrated between OAG and parity is surprising. A remote mechanism of cumulative glaucomatous optic nerve head damage during subsequent pregnancies could involve elevated placental corticotrophin

Table 4 Maximum intraocular pressure (IOP) (of two eyes) in women by use of hormone replacement therapy (HRT), adjusted for age and confounding factors, after excluding women currently using glaucoma medications

HRT	Participants (%)	IOP (mean (SEM))		Multivariate adjusted*	p Value
		Age adjusted	p Value		
Current use					
Yes	15.8	16.0 (0.2)		16.1 (0.2)	
No	74.7	16.5 (0.1)	0.03	16.5 (0.1)	0.09
Ever use					
Current	15.8	16.1 (0.2)		16.2 (0.2)	
Past	11.1	16.8 (0.2)	0.009	16.8 (0.2)	0.02
Never	63.6	16.4 (0.1)	0.06	16.4 (0.1)	0.20

*Adjusted for age, history of diabetes, hypertension, myopia, pseudoexfoliation, and family history of glaucoma.

releasing hormone levels during parturition.³⁴ This could lead to elevated endogenous plasma cortisol with potential to bind with trabecular meshwork receptors,³⁵ affect ocular aqueous outflow mechanisms and develop glaucoma in susceptible individuals.³⁶ Owing to other complex hormone related vascular alterations during pregnancy and parturition, definitive theories for this association are speculative.³³

Several investigators have documented lower IOP during pregnancy,^{37 38} and in multigravid compared with primigravid women.³⁹ The negative association found between parity and OH in our study thus questions whether pregnancy induced IOP reductions could be long standing. During pregnancy, high progesterone^{33 40} and increased aqueous outflow facility could assist in lowering IOP.

Interpreting associations with use of hormone replacement should be made with care because of the small numbers and limitation of our analyses in relation to the type of treatment. The Rotterdam Study,¹⁸ however, also reported similar non-significant reduced odds for OAG in hormone replacement users (odds ratio = 0.5). Although we did not find a relation between ever use of hormone replacement and OH, the maximum IOP between the two eyes was lower in current users, a finding supported by other studies.^{41 42}

Although our study was unable to confirm the association reported by the Rotterdam Study between OAG and earlier age at natural menopause, the positive finding in relation to later menarche does not allow us to exclude a possible role of endogenous female sex hormones in glaucoma. Our study also documents a possible relation between increased parity and glaucoma, although mechanisms underlying this are unclear.

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