



Oral Contraceptive Use and Prevalence of Self-Reported Glaucoma or Ocular Hypertension in the United States

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Purpose: To investigate the association between oral contraceptive (OC) use and glaucoma prevalence in the United States.

Design: Cross-sectional study.

Participants: A total of 3406 female participants, aged 40 years or older, from the 2005 to 2008 National Health and Nutrition Examination Survey, who reported a presence or absence of glaucoma or ocular hypertension completed both the vision and the reproductive health questionnaires and underwent eye examinations.

Methods: Multivariate regression analysis was used to assess the correlation between OC use and self-reported glaucoma or ocular hypertension (n = 231 cases), controlling for potential confounders, including age, ethnicity, systemic comorbidities such as hypertension and stroke, ocular diseases such as cataract and diabetic retinopathy, and reproductive health factors, including age at menopause, age at menarche, history of hormone replacement therapy, and gynecological surgical history.

Main Outcome Measures: The outcome variable was self-reported glaucoma or ocular hypertension.

Results: After adjusting for confounders, those with ≥ 3 years of OC use had greater odds (odds ratio, 1.94; 95% confidence interval, 1.22–3.07) of self-reported glaucoma or ocular hypertension. Other factors associated with higher glaucoma or ocular hypertension prevalence included older age, African American race, and later age at menarche.

Conclusions: Oral contraceptive use may be associated with increased risk of self-reported glaucoma or ocular hypertension. *Ophthalmology* 2016;■:1–8 © 2016 by the American Academy of Ophthalmology.

Glaucomatous disease is a leading cause of bilateral blindness worldwide, second only to cataract.¹ Known risk factors for glaucoma include family history, African American ethnicity, and older age.¹ Women are found to be more affected by this debilitating disease compared with their male counterparts.² Currently, the only confirmed modifiable risk factor for glaucoma is intraocular pressure (IOP), and IOP lowering is the target of all current medical and surgical therapies. Unfortunately, therapies aimed at lowering IOP are not always successful. Furthermore, because of the lack of highly effective treatment, little evidence exists to link early detection of glaucoma and preventable blindness or visual impairment. Identification of novel glaucoma risk factors may allow for earlier and more targeted screening of susceptible populations.

Estrogen is thought to play an important role in glaucoma pathogenesis.^{2,3} Although it has been hypothesized that early estrogen deficiency may increase the susceptibility to glaucomatous damage, the exact mechanism of how estrogen may protect the optic nerve remains unclear.² Estrogen receptors are expressed in a variety of ocular tissues, including retinal ganglion cells (RGCs), lens epithelial

cells, corneal epithelium, ciliary body, and iris stroma.^{4–7} Some have theorized that estrogen enhances nitric oxide signaling within the trabecular meshwork and in the retinal vasculature that supplies the optic nerve to favorably modify outflow facility and retinal autoregulation, respectively. In support of this alternative hypothesis, the relation between postmenopausal hormone (PMH) use and primary open-angle glaucoma (POAG) was modified by nitric oxide synthase 3 single nucleotide polymorphisms in a case control group nested within the Nurses' Health Study.⁸ In addition, evidence suggests that estrogen has direct beneficial effects on RGCs. One study showed that 17-beta-estradiol eye drop treatment reduced RGC and axon loss through inhibition of ganglion cell apoptosis in a rodent model of glaucoma.⁹ This study also demonstrated evidence of multiple, specific biochemical events that could account for estrogen-mediated RGC protection. Finally, it has been observed that estrogen and estrogen analogs are protective against insults in a mouse retinal photoreceptor cell line, suggesting that estrogen could emerge as a useful compound for neuroprotection of retinal cells.⁵

Previous clinical studies have shown an association between relative estrogen deficiency and glaucoma. In one

study, early age at menopause was associated with an increased risk of POAG, whereas later age at onset of menopause was associated with a decreased risk of POAG.¹⁰ Five-year oral contraceptive (OC) use, which alters the physiologic cycling of estrogen levels in women of reproductive age, was associated with a 25% increased risk of POAG in a prospective analysis of the Nurses' Health Study cohort.¹¹

In this study, we aimed to assess the association of OC use and prevalence of self-reported glaucoma or ocular hypertension in the United States using the National Health and Nutrition Examination Survey (NHANES).¹²

Methods

Sample and Population

Data from the 2005 to 2008 NHANES,¹² a cross-sectional series of interviews and examinations of the US civilian, noninstitutionalized population, were used to study the relationship between OC use and self-reported glaucoma or ocular hypertension. The NHANES is administered by the Centers for Disease Control and Prevention to provide US health statistics of approximately 5000 persons per year. It uses a stratified multistage sampling design that requires a weighting scheme to provide optimal estimates of disease prevalence among the US population. Our analysis included 3406 female participants in NHANES 2005–2008, who were aged 40 years or older and underwent both the interview (including both eye health and reproductive health questionnaires) and the examination portions of the study. There were 351 participants who were aged at least 40 years who did not answer the questions regarding history of OC use or self-reported history of glaucoma or ocular hypertension. These participants were excluded from analysis. As shown in Table 1, when compared with the excluded subjects, women included in this study were younger (57.4 vs. 60.9 years; $P = 0.0007$), had higher percentages of white participants ($P < 0.0005$), reported overall better health ($P = 0.01$), and had higher body mass index (BMI) (29 vs. 28.2 kg/m²; $P = 0.04$). The percentage of participants with vertical cup-to-disc ratio (CDR) >0.7 were not significantly different between the included and excluded participants ($P = 0.89$). Included participants showed a lower percentage of diabetic retinopathy ($P = 0.006$), cataract surgery ($P = 0.02$), and frequency doubling technology (FDT) defects ($P = 0.03$) in 1 or both eyes. However, this may be attributed to their significantly younger age and better general health conditions.

Measures

The primary exposure was self-reported OC use, categorized into the following 3 groups: denies OC use, <3 years of OC use, and ≥ 3 years of OC use. The NHANES included a reproductive health questionnaire to be answered by women who were aged 12 years and older at the time of a survey. These questions were asked at the Mobile Examination Center, during the Mobile Examination Center interview, using a computer-assisted personal interviewing system. Questions addressing age when first menstrual period occurred, age at last menstrual period, days since last period, history of pregnancy, number of total pregnancies, age at first live birth, and a history of breastfeeding, hysterectomy, bilateral oophorectomy, endometriosis or uterine fibroids, breast, uterine, or ovarian cancer, OC use, and hormone replacement therapy use were included in the questionnaire.

The primary outcome was the presence or absence of self-reported glaucoma or ocular hypertension. Potential confounding

variables included age, ethnicity, BMI, health-related behaviors such as smoking (current, past, or never); alcohol use (number of alcoholic drinks per day over the past year: >1 drink per day, <1 drink per day); comorbid medical conditions, such as self-reported history of hypertension or stroke; comorbid eye conditions, such as a self-reported history of cataract extraction surgery and diabetic retinopathy; general health condition (self-rated as excellent or very good, fair, or poor or very poor); and reproductive health condition, such as number of pregnancies, menopausal status, age at menarche, history of PMH use, history of hysterectomy or bilateral oophorectomy (including years since oophorectomy if answered yes), and history of breast, uterine, or ovarian malignancies.

The proportion of participants with a CDR >0.7 and the proportion of participants with at least 1 visual field defect in either eye based on FDT abnormalities, between the “yes glaucoma or ocular hypertension group” and the “no glaucoma or ocular hypertension group,” were used for internal validation of self-reported glaucoma or ocular hypertension. Both the percentage of participants with CDR >0.7 and the percentage of participants with at least 1 FDT defect in either eye were higher in the “yes” group compared with the “no” group (10.9% vs. 0.3%, $P < 0.001$; 22.3% vs. 6.4%, $P < 0.001$, respectively) (Table 2).

Analysis

We compared the distribution of possible confounding variables between participants with and without self-reported glaucoma using design-adjusted Rao–Scott Pearson-type chi-square and Wald tests for categorical and continuous variables, respectively.¹³ We used multiple imputation, a flexible, simulation-based statistical technique that is used to deal with missing data or survey nonresponse, which arises frequently in the NHANES data set.¹⁴ Multiple imputation was conducted using the mice (multiple imputation by chained equations) package, version 2.22. For each multiply imputed data set, OC use was always included in each statistical model, but backward stepwise regression was used for regressors other than OC. Backward stepwise regression on these other potential confounders was conducted by sequentially deleting the regressor (other than OC use with the largest estimated P value, and continuing until all remaining other regressors yielded $P < 0.25$). Different values for the P value for stepwise deletion have been used in the literature, and a value of $P < 0.1$ is frequently used.¹⁵ However, we used a relatively conservative threshold ($P < 0.05$) that favors the inclusion of predictors other than OC use. The OC use regressors were included in all models and not subject to stepwise regression. The estimated regression coefficients for OC regressors, standard errors, and hypothesis tests for these coefficients were conducted using the standard Rubin procedure.¹⁶ Sixty-four multiple imputations were used. Computations were conducted in R version 3.1 for MacIntosh (R Foundation for Statistical Computing, Vienna, Austria, using the procedure svyglm from the R package survey for survey weighted analysis, and the package mice for multiple imputation).

Results

The 2005–2008 NHANES data yielded a total of 3406 female participants, aged 40 years or older, who participated in both the interview and the examination portions of the study, including the reproductive health questionnaire, and all answered the question regarding whether or not they had ever been informed of a diagnosis of “glaucoma or high pressure in the eyes” (referred to as “history of self-reported glaucoma” in the following sections) by a health professional. Of all included participants, 231 self-reported a

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