

THE SYSTEMATIC REVIEW OF GLAUCOMA AND ITS ASSOCIATIONS WITH FEMALE REPRODUCTIVE FACTORS

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ABSTRACT

Background: Estrogen may have a neuroprotective role in glaucoma, and estrogen insufficiency is thought to contribute to glaucomatous damage through both mechanical and vascular processes.

Methods: By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2014 and 2024 were taken into account. Several different online reference sources, like Pubmed and SCIENCE DIRECT, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

Result: In the PubMed database, the results of our search brought up 93 articles, whereas the results of our search on SCIENCE DIRECT brought up 76 articles. The results of the search conducted for the last year of 2014 yielded a total 41 articles for PubMed and 26 articles for SCIENCE DIRECT. In the end, we compiled a total of 6 papers, 4 of which came from PubMed and 2 of which came from SCIENCE DIRECT. We included six research that met the criteria.

Conclusion: In summary, a longer duration of OC usage may be related with a higher risk of OAG; however, it is unclear if OC use in general raises the risk of OAG or whether this potential association is mediated by IOP. An earlier age at natural menopause may increase the incidence of OAG. Most significantly, PMH use may be related with a lower IOP, and the estrogen-only kind of PMH may be associated with a lower risk of OAG.

Keyword: Estrogen, Female reproductive factors, Glaucoma, Trai

INTRODUCTION

Glaucoma is the main cause of permanent blindness globally, and it is distinguished by gradual loss of visual function and retinal ganglion cells (RGC). Current epidemiological, clinical, and basic scientific evidence suggests that estrogen contributes to the aging of the optic nerve. Menopause, a crucial biological life event for all women, is accompanied by a decrease in circulating sex hormones such as estrogen. While 59% of the glaucomatous population is female, gender is not considered a risk factor for getting glaucoma.¹

Although POAG can occur at any IOP level, ocular hypertension (OHT) remains a significant incidental risk factor for acquiring this condition, with OHT defined as an IOP greater than 21 mmHG. While IOP remains a significant risk factor for the development and progression of glaucoma, there are undoubtedly other, as yet undiscovered, mechanisms that contribute to the development and progression of glaucomatous optic neuropathy. In this review, we investigate the possibility of menopause as a sex-specific risk factor for developing glaucoma. Based on our findings and those of other researchers, we argue that menopause and estrogen signaling can alter IOP and aqueous humor outflow resistance, two parameters known to be involved in the pathogenesis of glaucoma.²

Understanding how menopause affects the development and progression of glaucoma might help clinicians make decisions when evaluating a woman with glaucoma or a glaucoma suspect. Given the effects of menopause on IOP, a clinician's decision on whether to commence IOP lowering medicines and what therapeutic IOP target to utilize may be influenced by a woman's reproductive status (i.e., premenopausal, perimenopausal, or postmenopausal). Furthermore, and perhaps more importantly, better understanding of the effects of menopause and estrogen signaling on glaucoma would most likely lead to new targets for glaucoma treatment.¹

Furthermore, because estrogen is known to be neuroprotective, it could play a role in the treatment of non-glaucomatous ocular neuropathies such as ischemia, compressive, and traumatic optic neuropathy. There is a growing corpus of literature on the relationship between menopause and glaucoma. The similarities between menopause (or ovariectomy) in glaucoma and other major illnesses support the idea that menopause, a significant life event in women, may be a sex-specific risk factor for glaucoma onset and/or progression. Furthermore, in ocular research, the consistency across laboratories, animal models, and other damage models supports the hypothesis of menopause as a sex-specific risk factor for developing glaucoma that requires further investigation.¹

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we review published literature contains the associations of female reproductive factors and glaucoma. This is done to provide an explanation and improve the handling of treatment at the patient. As the main purpose of this paper, to show the relevance of the difficulties that have been identified as a whole.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements:

1) The paper needs to be written in English. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "female reproductive factors" and "glaucoma" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SCIENCE DIRECT databases by inputting the words: *("femal"[All Fields] OR "female"[MeSH Terms] OR "female"[All Fields] OR "females"[All Fields] OR "female s"[All Fields] OR "femals"[All Fields]) AND ("reproduction"[MeSH Terms] OR "reproduction"[All Fields] OR "reproductions"[All Fields] OR "reproductive"[All Fields] OR "reproductively"[All Fields] OR "reproductives"[All Fields] OR "reproductivity"[All Fields]) AND ("factor"[All Fields] OR "factor s"[All Fields] OR "factors"[All Fields]) AND ("glaucoma"[MeSH Terms] OR "glaucoma"[All Fields] OR "glaucomas"[All Fields] OR "glaucoma s"[All Fields]) AND ((humans[Filter]) AND (2014:2024[mdat]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to

the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

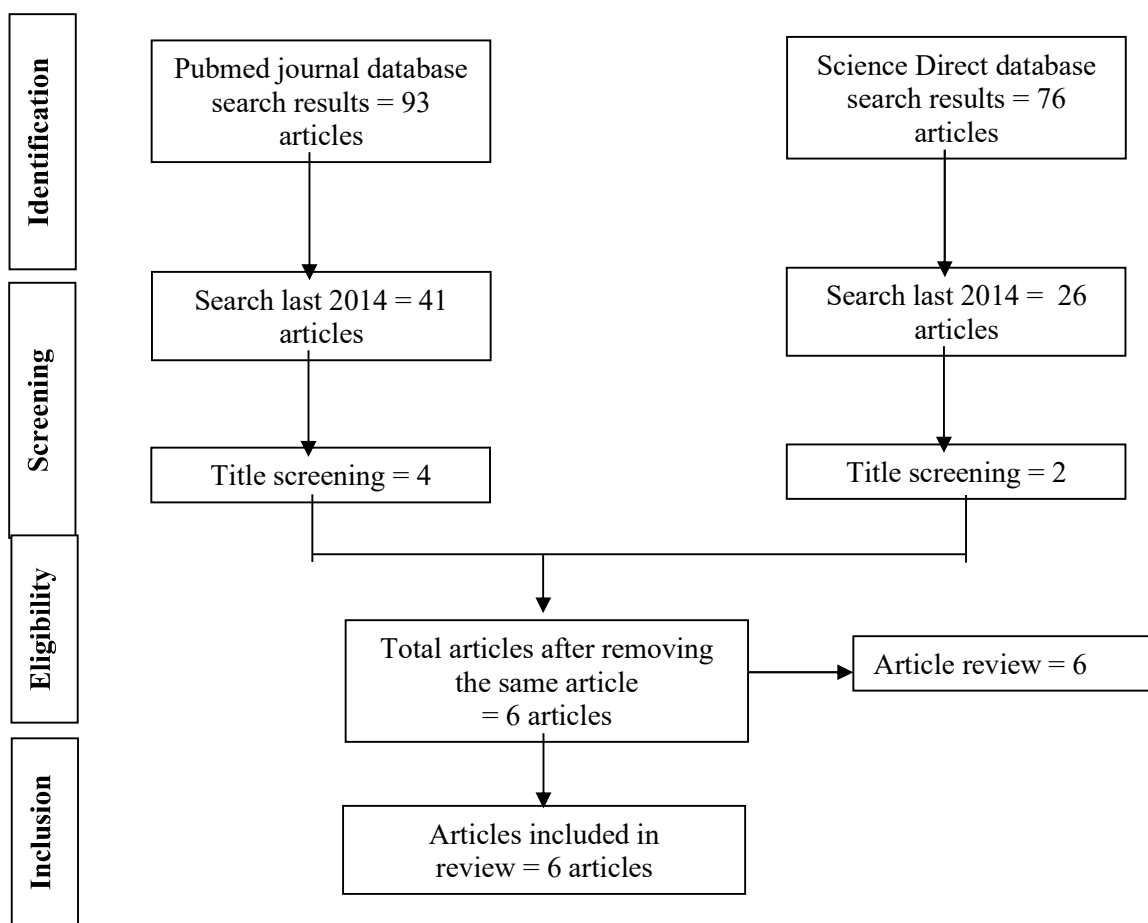


Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 93 articles, whereas the results of our search on SCIENCE DIRECT brought up 76 articles. The results of the search conducted for the last year of 2014 yielded a total 41 articles for PubMed and 26 articles for SCIENCE DIRECT. In the end, we compiled a total of 6 papers, 4 of which came from PubMed and 2 of which came from SCIENCE DIRECT. We included six research that met the criteria.

Lee, et al³ (2019) showed that a history of three or more deliveries, as well as a first-time delivery age of less than 23 years, were linked to an elevated risk of OAG. These findings imply that changes or events from pregnancy until delivery influence the development of glaucoma.

Shin, et al⁴ (2018) showed that only early menopause was related with an increased risk of open angle glaucoma, whereas earlier Western studies identified both early menopause and late menarche as risk factors.

Lam, et al⁵ (2014) showed that women who had menopause at a younger age were more likely to have glaucoma. This association needs to be confirmed in other studies.

Table 1. The literature include in this study

Author	Origin	Method	Sample	Result
Lee et al, 2019 ³	South Korea	Cross sectional study	1798 patients	The prevalence of OAG among study participants was 6.42%. There was a significant difference in the number of deliveries and age at first delivery between the OAG group and the nonglaucoma group. In multiple linear regression models adjusted for age, hypertension, and intraocular pressure only pregnancy 1 was associated with higher risk of OAG compared with pregnancy 2 (P=0.023). Subjects who had 3 or 4 deliveries were at higher risk of OAG compared with subjects with 2 deliveries (P=0.027). An age at first delivery of 16 to 20 years or 21 to 23 years was associated with increased OAG risk compared with the reference group (P<0.05).
Shin et al, 2018 ⁴	South Korea	Cross sectional study	6860 patients	Of the enrolled participants, 6,860 participants (397 with OAG and 6,463 without OAG) met our study criteria and were included in the analyses. In the multivariate logistic regression analysis after adjusting for all potential confounding factors, only early menopause (younger than 45 years) was significantly associated with OAG in participants with natural menopause (OR 2.28, 95% CI 1.17–4.46). Age at menarche, parity, history of lactation, and administration of OC or HRT were not significantly associated with OAG.
Lam et al, 2014 ⁵	Singapore	Cross sectional study	1176 patients	A total of 1176 women reported having experienced menopause by the time of the study with 1073 (91%) having a natural menopause, 88 (7.5%) a hysterectomy and 9 (0.8%) due to other reasons; HRT was used by 70 (6%) women. Women whose age at

				menopause was ≤ 52 years were 3.5 times more likely to have glaucoma (95% confidence interval, CI, 1.23-9.98, p value = 0.02) than those whose age at menopause was ≥ 53 years. Age of menopause was not associated with AMD (age-adjusted odds ratio, OR, 1.22, 95% CI 0.65-2.31), diabetic retinopathy (age-adjusted OR 1.01, 95% CI 0.66-1.54) or cataract (age-adjusted OR 1.38, 95% CI 0.95-2.00). Use of HRT was not associated with any of these eye diseases.
Vajaranant et al, 2014⁶	USA	Cross sectional study	1044 patients	Of 1,044 women who underwent bilateral oophorectomy before menopause, 147 developed glaucoma. Of 1,070 referent women, 133 developed glaucoma. Women who underwent bilateral oophorectomy showed no increased risk of glaucoma in the overall group (HR 1.12, 95% CI 0.89–1.42). However, women who underwent oophorectomy before age 43 years (n=344; the first tertile) had a significantly increased risk of glaucoma (HR 1.60, 95% CI 1.15–2.23). The results did not change after adjustment for hypertension, obesity, diabetes, or disorders of lipid metabolism at baseline. Approximately 11% of women with bilateral oophorectomy before age 43 years were treated with estrogen to age 50 years; however, treatment did not reduce the association (HR 1.59, 95% CI 0.81–3.13).
Newman-Casey et al, 2014⁷	USA	Retrospective longitudinal cohort study	152.163 patients	Of 152,163 eligible enrollees, 2925 (1.9%) developed POAG. After adjustment for confounding factors, each additional month of E was associated with a 0.4% reduced risk for POAG (HR=0.996, [CI, 0.993–0.999], p=0.02). The risk for POAG did not differ with each additional month of E+P (HR=0.994, [CI, 0.987–1.001], p=0.08) or E+A (HR=0.999 [CI, 0.988–1.011], p=0.89) use.

<p>Vajaranant et al, 2018⁸</p>	<p>USA</p>	<p>Randomized controlled study</p>	<p>25,535 patients</p>	<p>After excluding women with prevalent glaucoma or without claims for eye-care provider visits, the final analysis included 8,102 women (mean age=68.5±4.8 years). The OAG incidence was 7.6% (mean follow-up=11.5±5.2 years; mean HT duration=4.4±2.3 years). Increased age (p-trend=0.01) and African-American race (HR=2.69, 95%CI=2.13 to 3.42; Caucasian as a reference) were significant risk factors for incident OAG. We found no overall benefit of HT in reducing incident OAG (HR=1.01, 95%CI=0.79–1.29 in the CEE trial, and HR=1.05, 95%CI=0.85–1.29 in the CEE+MPA trial). However, race modified the relationship between CEE use and OAG risk (p-interaction=0.01), and risk was reduced in African-American women treated with CEE (HR=0.49, 95%CI=0.27–0.88), compared to placebo. Race did not modify the relation between CEE+MPA use and OAG risk (p-interaction=0.68).</p>
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Vajaranant, et al⁶ (2014) showed that early bilateral oophorectomy increases the risk of a number of health outcomes, including various brain aging-related diseases. This is the first study to reveal that women who underwent bilateral oophorectomy before the age of 43 have an increased chance of acquiring glaucoma. These findings are consistent with earlier epidemiologic, clinical, and animal investigations that indicate estrogen has a neuroprotective impact on the optic nerve. The findings give new data to support the personalized assessment of sex-specific risk factors for glaucoma, and may aid women and their physicians in considering the risks and advantages of bilateral oophorectomy.

Newman-Casey, et al⁷ (2014) showed that postmenopause hormone (PMH) usage may increase women's chance of developing glaucoma. More research is needed to better understand the intricate link between PMH consumption and glaucoma. Additional research should investigate if the risk of primary open angle glaucoma (POAG) is affected solely by E or by any PMH class. Ongoing research into how estrogen affects retinal ganglion cells (RGC) layer apoptosis may eventually lead to the discovery of new mechanisms by which sex hormones affect POAG, as well as novel, non-oral routes of PMH administration that may further reduce the risk of POAG.

Vajaranant, et al⁸ (2018) showed that conjugated equine estrogens (CEE) intervention for four years was related with a 50% reduction in the risk of OAG in postmenopausal African-American women after hysterectomy over a 12-year period. Our findings further imply that the sex-hormone-related pathophysiology of glaucoma may inform customized assessments of the hazards and benefits of hormone therapy (HT) in older menopausal women.

DISCUSSION

This systematic review involved a total of 188,576 data of female patients that potentially have associations of the reproductive factors with cases of glaucoma. Estrogen may have a neuroprotective role in glaucoma, and estrogen insufficiency is thought to contribute to glaucomatous damage through both mechanical and vascular processes.

A younger age at menarche should theoretically result in more overall lifetime estrogen exposure, leading to a lower chance of POAG. However, the evidence from the included observational studies suggests that there is no obvious link between menarche age and POAG risk. The association between age of menarche and POAG should be further explored, taking into account the full female reproductive and postreproductive history.⁴

Observational studies imply that there is no direct association between the number of term pregnancies and the risk of POAG. Although the Blue Mountains Eye Study and the Korean National Health and Nutrition Examination Survey (NHANES)³⁵ reported that higher numbers of pregnancies were associated with higher risks of POAG, these findings were not replicated in other studies, and no consistent trend was found between increasing parity and increasing risks of POAG.^{3,4}

Although the current data does not show a direct link between OC usage and glaucoma-related features, potential negative relationships with length of use have been observed. The nature of the relationship between ever or current OC usage and OAG is still being investigated, but NHS findings show a probable link between longer duration of use and increased POAG risks in particular.⁹

Women's contraception decisions are influenced by a variety of demographic, social, and regional factors, which may explain or modify any potential connections between OC use and IOP/OAG. The contradictory relationships discovered in research examining parity and OC usage could be attributed to the age range during which OC use commonly occurs vs the typically older age of glaucoma onset. This makes it difficult to discover robust and consistent relationships across research. Furthermore, no large-scale studies have been undertaken to investigate the relationship between OC consumption and IOP, leaving this a highly fruitful field for future research.^{10,11}

The epidemiology research does not consistently support an overall link between age at menopause and POAG; nevertheless, some subgroup analyses indicate that people with an earlier age at natural menopause are more likely to develop POAG. Menopause can occur naturally or be caused with surgery or radiation. Each of these forms of menopause has the potential to alter menopause age, although their exact implications are not yet fully understood. Although confounding by surgical indication cannot be completely eliminated, this study's discovery that menopause induced at a young age may raise the incidence of glaucoma provides credence to the role estrogen insufficiency may have in glaucoma pathophysiology.¹⁰

Ages at menarche and menopause serve as surrogate factors for years of reproductive length, which is a more direct (although imperfect) indicator of endogenous estrogen exposure. The relationship between the duration of reproductive years and POAG risks is unknown, and future studies of the role of reproductive years in glaucoma pathogenesis may benefit from the establishment of genetic risk scores that account more correctly for endogenous estrogen exposure.²

Estrogen levels gradually fall during the reproductive years and after menopause. Postmenopausal women are thus theoretically at a higher risk of glaucoma and related features, which might be reduced by using exogenous estrogen supplementation. Future genetic epidemiology research may shed light on race as a potential modulator of the relationship between estrogen-only PMH usage and POAG, as well as whether similar correlations hold true for the association with IOP.²

Several significant sources of heterogeneity and potential bias were detected throughout the included studies, making direct comparison of the findings difficult and ultimately preventing a formal statistical synthesis of the data. Different study designs were used (including cross-sectional, longitudinal, and RCT designs), participants were from a variety of nations and ethnicities, and analyses did not consistently account for the same covariates. Although most studies assessing relationships with OAG controlled for age and, in many cases, other socioeconomic or medical covariables, residual confounding from unmeasured covariables remains a possibility, which means that the detected associations could be driven by unknown or unmeasurable factors.¹

There is an obvious need for more research into the relationships between female reproductive variables and glaucoma and related features. As the prevalence of OAG is expected to rise in the coming years, research into sex-specific risk factors and gene-environment interactions will be critical to improving our understanding of OAG's associations and pathogenesis, potentially leading to novel preventative measures and therapies.

CONCLUSION

In summary, a longer duration of OC usage may be related with a higher risk of OAG; however, it is unclear if OC use in general raises the risk of OAG or whether this potential association is mediated by IOP. An earlier age at natural menopause may increase the incidence of OAG. Most significantly, PMH use may be related with a lower IOP, and the estrogen-only kind of PMH may be associated with a lower risk of OAG.

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