SURABAYA MEDICAL JOURNAL
(SMJ IDI SURABAYA)
Volume 3, Issue 2, 2025, p.43-51
eISSN: 2986-7584
pISSN: 2986-2469

SYSTEMATIC REVIEW

Female Reproductive Factors as Risk of Open-Angle Glaucoma: A Systematic Review

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Article Info

Article history:
Received : 30-10-2025
Revised: 17-06-2026
Accepted: 22-07-2026
Published : 06-08-2026

Keywords:
Estrogen;
Female reproductive factor;
Human and health;
Menopause;
Open-angle glaucoma.

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ABSTRACT

Background: Glaucomatous optic neuropathy arises through multifactorial vascular and mechanical pathways, and estrogen is thought to play a neuro-modulatory role protecting retinal neurons. Given that women constitute a majority of glaucoma patients worldwide, the influence of female reproductive factors on open-angle glaucoma (OAG) risk warrants systematic evaluation. **Objective:** This systematic review aims to examine the correlation between female reproductive factors such as age at menarche, parity, menopause, and postmenopausal hormone (PMH) use and the risk of developing OAG. **Methods:** In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines, a comprehensive literature search was performed in PubMed and ScienceDirect databases for studies published between 2010 and 2025. Eligible studies included original articles in English that examined reproductive factors and OAG in adult women. **Result:** The initial search identified 3080 articles from PubMed and 208 from ScienceDirect. After screening, only five studies met the inclusion criteria. Overall evidence indicates an association between earlier onset for natural menopause and increased OAG risk, while estrogen-only PMH use may offer a protective effect, particularly among African-American women. **Conclusion:** Evidence suggests that female reproductive history may influence the risk of OAG. Early menopause appears to increase OAG susceptibility, whereas estrogen-only hormone therapy might reduce it. Given the limited number and heterogeneity of available studies, further large-scale, well-controlled research is needed to clarify these associations.

Citation:
Gunawan, A. C. V., Kuhurina, B., Atin, F. (2026). Female Reproductive Factors as Risk of Open-Angle Glaucoma: A Systematic Review. Surabaya Medical Journal, 3(2): 43-51.
DOI: https://doi.org/10.59747/smjidisurabaya.v3i2.120

Surabaya Medical Journal (SMJ IDI SBY)
eISSN: 2986-7584; pISSN: 2986-2469; DOI: https://doi.org/10.59747/smjidisurabaya.v3i2.120

Highlights

1. Early menopause is associated with an increased risk of open-angle glaucoma.
2. Estrogen-only postmenopausal hormone therapy may reduce open-angle glaucoma risk in selected populations.

BACKGROUND

Glaucoma remains the primary reason of irreversible blindness globally, characterized by gradual optic nerve damage and a loss of retinal ganglion cells (RGCs). Primary open-angle glaucoma (POAG) is the most common type. Although intraocular pressure (IOP) is the most established modifiable risk factor, other factors including vascular, mechanical, and hormonal also contribute to its pathogenesis (Neustaeter et al., 2021).

Estrogen, a female sex hormone, has been suspected to have neuroprotectitive and vascular regulator function. Its decline during menopause, a biological occasion in aging women, may influence optic nerve susceptibilities to damage. Epidemiologic data reveal that women constitute around 60% of glaucoma cases; however, gender itself is not recognized as a direct risk factor. Understanding how reproductive stages such as menarche, parity, menopause, and hormone therapy relate to OAG risk may enhance glaucoma management and prevention strategies (Madjedi et al., 2022; Neustaeter et al., 2021).

Although several epidemiological studies have investigated the relationship between female reproductive history and glaucoma, the reported findings remain inconclusive. Variations in study populations, definitions of reproductive factors, and outcome measures have contributed to inconsistent results. Furthermore, evidence regarding the combined influence of menarche, parity, menopause, and postmenopausal hormone therapy on open-angle glaucoma has not been comprehensively synthesized. Therefore, this systematic review was conducted to summarize the current evidence and identify areas requiring further investigation. (Madjedi et al., 2022; Neustaeter et al., 2021).

OBJECTIVE

This systematic review aims to examine the association between female reproductive factors such as age at menarche, parity, menopause, and postmenopausal hormone (PMH) use and the risk of developing OAG.

MATERIAL AND METHODS

Protocol

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 declaration to guarantee methodological transparency. The review protocol outlined the research objectives, inclusion criteria, and data extraction methods.

Criteria for Eligibility

Studies were included if they examined female reproductive factors (including menarche, menopause, parity, or PMH utilization) in relation to open-angle glaucoma, were released between 2010 and 2025 in peer-reviewed journals, and were written in English and provided sufficient quantitative or qualitative data. Exclusion criteria included review articles, conference abstracts, editorials, duplicate publications, or studies lacking DOI or full-text availability.

Surabaya Medical Journal (SMJ IDI SBY)
eISSN: 2986-7584; pISSN: 2986-2469; DOI: https://doi.org/10.59747/smjidisurabaya.v3i2.120

Search Strategy

We applied "female reproductive factor" and "open angle glaucoma" as keywords. The search for publications to be included in the systematic review proceeded by searching the PubMed and SCIENCE DIRECT databases through input of the words: *("female" OR "reproductive factor") AND ("open-angle glaucoma" OR "glaucoma")* used in searching the literature.

Study Selection and Data Extraction

Two reviewers individually assessed titles and abstracts to determine relevance. Full-text studies were obtained for articles which fullfilled the inclusion criteria. Disputes were resolved through compromising. The data gathered covered the author, publication year, study design, sample size, population characteristics, and main outcomes related to OAG risk.

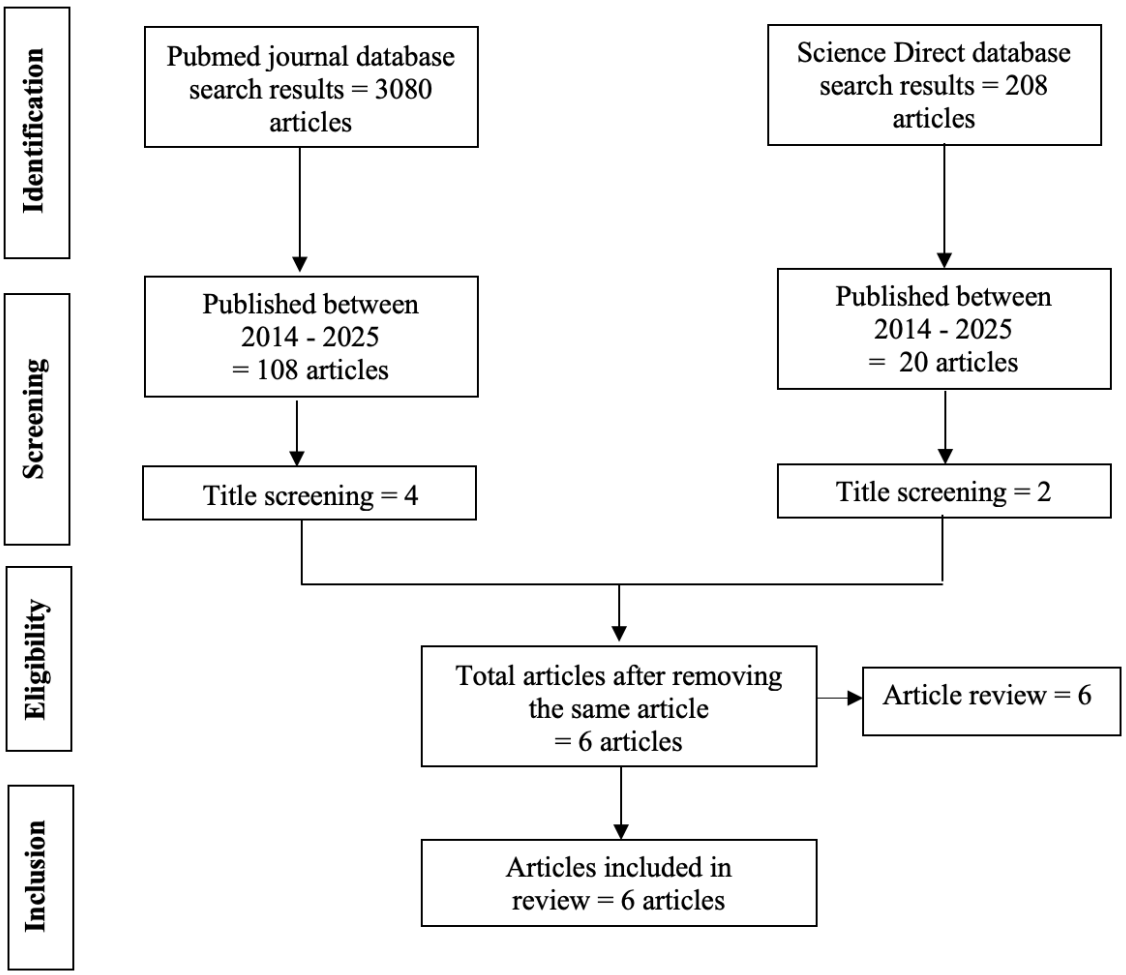

Figure 1. PRISMA Article Search Flowchart

From 3,080 PubMed records, 108 articles remained after publication year filtering. Title and abstract screening excluded studies unrelated to female reproductive factors or glaucoma, leaving four eligible studies for full-text review. From 208 ScienceDirect records, 20 articles remained after publication year filtering, and two studies were considered potentially relevant after title and abstract screening. Following duplicate removal and full-text eligibility assessment, five studies met all inclusion criteria and were included in the final review.

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Quality Assessment and Data Synthesis

The quality and risk of bias were evaluated using established domain-based assessment tools according to study type (e.g., observational or interventional). Studies with high risk of bias or unclear methodological reporting were interpreted with caution during synthesis.

RESULTS

The database search yielded 3,080 articles from PubMed and 208 from ScienceDirect. After filtering duplicates and non-relevant papers, five studies met the inclusion criteria: four from PubMed and one from ScienceDirect.

A study by Lee et al (2019) showed that there is little data to support the hypothesis that optic disc characteristics in early adulthood are correlated with female reproductive variables. Considering the modest number of parous women in the available sample, the substantial link between parity and optic disc parameter deserves more research. We will be able to investigate any relationships between these characteristics and optic disc metrics as well as the risk of glaucoma in later life through follow-ups with this group.

Vajaranant et al (2018) found that after a hysterectomy, postmenopausal African American women who had 4-year conjugated equine estrogens (CEE) intervention had a half-decreased incidence of open angle glaucoma (OAG) during a 12-year follow-up period. Our results also point to a possible link between sex hormones and the pathogenesis of glaucoma, which should inform tailored evaluations of the advantages and disadvantages of hormone therapy (HT) for older menopausal women. There should be more research done.

Numerous health consequence, including various disorders linked to brain aging, are more prevalent after an early bilateral oophorectomy. This is the first research by Vajaranant et al (2014) that demonstrating the higher risk of glaucoma in women who had bilateral oophorectomy prior to the age of 43. These results corroborate with epidemiological, clinical, and animal research indicating that estrogen protects the optic nerve from damage. The findings in this study provide the new data that favor the customized evaluation of sex-specific glaucoma risk factors and might help women and their doctors weigh the advantages and disadvantages of bilateral oophorectomy.

Table 1. The Literature Included in This Study

AUTHOR	ORIGIN	METHOD	SAMPLE	RESULT
(Lee et al., 2019)	Australia	Retrospective study	494 patients	• Parous women had significantly greater vertical neuroretinal rim width than nulliparous women ($P < 0.001$). • Parous women showed significantly lower vertical and horizontal cup-to-disc ratios compared with nulliparous women (both $P < 0.001$). • The observed cup-to-disc ratios were inversely associated with neuroretinal rim width. • No significant association was found between age at menarche and optic disc parameters. • Hormonal contraceptive use was not significantly associated with optic disc measurements.
(Vajaranant et al., 2018)	USA	Randomized controlled study	8102 patients	• The incidence of OAG was 7.6% among 8,102 postmenopausal women during a mean follow-up of 11.5 years. • African-American race and increasing age were significant risk factors for OAG development.

Surabaya Medical Journal (SMJ IDI SBY)
eISSN: 2986-7584; pISSN: 2986-2469; DOI: https://doi.org/10.59747/smjidisurabaya.v3i2.120

				• Overall, hormone therapy (HT) did not significantly reduce the incidence of OAG. • Estrogen-only therapy (CEE) was associated with a lower risk of OAG among African-American women compared with placebo. • No race-specific effect was observed for combined estrogen–progestin therapy (CEE+MPA).
(Vajaranant et al., 2014)	USA	Cross sectional study	1044 patients	• Bilateral oophorectomy was not associated with a significantly increased overall risk of glaucoma (HR 1.12, 95% CI 0.89–1.42). • Women who underwent bilateral oophorectomy before the age of 43 had a significantly higher risk of glaucoma (HR 1.60, 95% CI 1.15–2.23). • The association remained significant after adjustment for diabetes, obesity, hypertension, and lipid disorders. • Postoperative estrogen therapy did not significantly reduce the increased glaucoma risk associated with early oophorectomy.
(Lam et al., 2014)	Singapore	Cross sectional study	1176 patients	• Most participants experienced natural menopause (91%), while 7.5% underwent hysterectomy-induced menopause. • Earlier age at menopause was associated with a higher risk of glaucoma (OR 3.51, 95% CI 1.23–9.98). • Hormone replacement therapy (HRT) was not significantly associated with glaucoma risk. • HRT use was also not associated with age-related macular degeneration, cataract, or diabetic retinopathy.
(Shin et al., 2018)	South Korea	Cross sectional study	6860 patients	• Premature menopause before 45 years of age was significantly associated with OAG (OR 2.28, 95% CI 1.17–4.46). • The association remained significant after adjustment for potential confounding factors. • Parity and breastfeeding history were not significantly associated with OAG. • Age at menarche, oral contraceptive use, and hormone replacement therapy showed no significant association with OAG risk.

Lam et al., (2014) demonstrated that younger women experiencing menopause displayed an elevated probability of developing glaucoma. Further research is necessary to validate this link.

Shin et al., (2018) reported that unlike previous Western studies that reported earlier menopause and later menarche as related variables, in this study found that only early menopause was linked with an elevated risk of OAG

DISCUSSION

This systematic review included data from 17,860 female patients from five studies to examine how reproductive factors relate to the development of open-angle glaucoma (OAG). Overall, the findings suggest that female reproductive history, particularly age at menopause, parity, and cumulative estrogen exposure, may influence glaucoma risk, with earlier estrogen loss tending to increase vulnerability of the optic nerve.

Theoretically, an earlier onset of menarche should increase lifetime estrogen exposure and thereby lower the risk of primary open-angle glaucoma (POAG). However, across the included studies, no clear

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linear association was identified, and no study specifically evaluated the relationship between menarche age and intraocular pressure (IOP). (Shin et al., 2018), examined several reproductive variables and found that age at menarche was not convincingly linked to glaucoma risk, likely in part because heterogeneity in study design and variable definitions prevented a robust pooled analysis. This is in contrast with the earlier meta-analysis Blue Mountains Eye Study that reported that late menarche (>13 years) was associated with an increased risk of OAG, and that higher parity similarly increased glaucoma prevalence, supporting the hypothesis that lower cumulative estrogen exposure may contribute to OAG development. An updated study needs to be done to further analysis this phenomenon (Lee et al., 2003).

The findings regarding parity in the present review differ from those reported in the Blue Mountains Eye Study. Lee et al. (2003) observed that higher parity was associated with an increased prevalence of open-angle glaucoma, suggesting that reproductive history may influence glaucoma risk. In contrast, the studies included in this review did not demonstrate a clear association between parity and OAG. Lee et al. (2019) reported differences in optic disc parameters between parous and nulliparous women, whereas Shin et al. (2018) found no significant relationship between parity and OAG risk. These discrepancies may reflect differences in study populations, outcome definitions, and methodological approaches.

The conflicting findings highlight an important knowledge gap regarding the role of parity in glaucoma development. Although parity has been proposed as a potential factor for hormonal exposure, current evidence remains insufficient to determine whether it independently contributes to OAG risk. Furthermore, most available studies have been observational and have used different classifications of reproductive history, limiting direct comparisons across studies. Future prospective studies with standardized definitions and adjustment for relevant hormonal and demographic factors are needed to clarify the relationship between parity and glaucoma risk.

Age at menopause appears as one of the most prominent factors in this review. (Lam et al., 2014) demonstrated a clear association between earlier menopause and increased probability of OAG. In their study, women who experienced premature menopause had a significantly higher risk of OAG compared with those whose menopause occurred at or after about 53 years of age. This evidence supports the idea that a shorter duration of endogenous estrogen exposure accelerates optic nerve susceptibility. A study by a more recent U.S. national cohort of female veterans showed that women with early menopause were diagnosed with glaucoma about six years earlier on average, and that each additional year before menopause was associated with an approximately one-year delay in glaucoma onset. Together, these studies provide evidence that the timing of menopause, and thus duration of estrogen exposure, influences the onset of glaucoma (Hogan et al., 2024; Lam et al., 2014).

At the same time, epidemiologic data do not uniformly show a simple, overall association between age at menopause and POAG across all populations. Menopause may be natural or induced (for example, via surgery or radiation), and these differing mechanisms can alter the timing of estrogen withdrawal and introduce confounding factors that are difficult to fully control. Some cohort and case–control studies found no significant overall association between age at natural menopause and POAG, yet subgroup analyses repeatedly indicated that women with very early or premature menopause had higher rates of glaucoma. This pattern supports the idea that the extremes of estrogen deprivation are most relevant clinically, even if more modest variation within the normal menopausal age range is harder to detect (Douglass et al., 2023; Hoopes et al., 2018).

(Vajaranant et al., 2014) evaluated medically induced menopause rather than natural menopause and focused on a comparatively young menopausal population (<43 years). Although the analysis was underpowered and did not show a statistically robust overall association, it suggested that menopause occurring at a very young age may increase glaucoma prevalence. Because these women often undergo oophorectomy or other interventions for serious gynecologic conditions, surgical and systemic factors

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may confound the relationship, but the study still offers important evidence that abrupt and early estrogen loss could contribute to glaucomatous damage.

Besides endogenous hormones, several studies have explored postmenopausal hormone therapy (PMH). (Vajaranant et al., 2018) extended an earlier randomized controlled trial by performing race-stratified analyses of estrogen-only PMH use. While there was no overall association between estrogen-only PMH and OAG in the pooled cohort, the subgroup analysis revealed a significant reduction in OAG risk among Black women using estrogen-only PMH, whereas no association was seen in White women. This suggests that genetic, vascular dysregulation, or race-related factors may modify the effect of exogenous estrogen on glaucoma risk. These findings also support the idea that universal recommendations on hormone therapy may not be appropriate across different ethnic groups.

Additional observational study has examined the wider profile of women with glaucoma. A recent review noted that female glaucoma patients tend to exhibit more vascular dysregulation and are more susceptible to ocular surface toxicity from topical glaucoma medications, raising further sex-specific therapeutic considerations. These factors may interact with hormonal history and estrogen status, further complicating the risk landscape (Madjedi et al., 2022; Rizk et al., 2024).

At the molecular and endocrine level, estrogen naturally exists in three principal forms: 17β-estradiol (E2), estrone (E1), and estriol (E3); all synthesized from androgenic precursors (testosterone and androstenedione) via aromatase. In premenopausal women, the ovaries are the main source of estrogen, although local intracrine synthesis from dehydroepiandrosterone (DHEA) occurs in many tissues. After menopause, ovarian production ceases, and extraovarian tissues become the sole source of circulating estrogen. Estrogen receptors in ocular tissues including the retina, trabecular meshwork, and Schlemm's canal, have been well documented, and membrane-associated estrogen receptors (mERs) further mediate rapid, non-genomic signaling. Genetic and molecular studies show that estrogen signaling regulates various IOP-related genes in the conventional outflow pathway, and 17β-estradiol has been detected in the aqueous humor, supporting a direct influence of estrogen on aqueous outflow resistance and IOP regulation (Labrie, 2015; Ozcan et al., 2017; Renoir et al., 2013; Youngblood et al., 2021; Zhang and Trudeau, 2006).

Progesterone may also affect the ocular system. Its antiglucocorticoid properties are thought to counteract the ocular hypertensive effects of endogenous corticosteroids, potentially contributing to lower IOP. However, the exact role of progestogens in IOP modulation is not well defined, and in some contexts progesterone may attenuate the IOP-lowering influence of estrogen. In a non-randomized active-controlled study, women receiving transdermal estradiol experienced a significant reduction in IOP, whereas those treated with oral conjugated equine estrogens plus progesterone did not, suggesting that route of administration and the addition of progestogens may alter the ocular response to hormone therapy (Fotesko et al., 2022; Ozcan et al., 2017)

In conclusion, current evidence suggests a possible association between female reproductive factors and open-angle glaucoma risk. Menopause-related factors appeared to have a more apparent association with glaucoma than other reproductive variables. However, the limited number of available studies and their methodological heterogeneity warrant cautious interpretation of these findings. Further research is required to better understand the relationship between reproductive factors and glaucoma development.

CONCLUSION

This systematic review provides evidence supporting a potential relationship between female reproductive factors and open-angle glaucoma risk. Early menopause appears to be the most consistent predictor of increased risk, whereas estrogen-only hormone therapy may offer partial protection. Further large-scale studies are needed to explore the hormonal mechanisms for glaucoma pathogenesis and to identify opportunities for gender-specific, especially female, prevention and therapy.

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Strength and Limitiation

This systematic review focuses on current evidence exploring the relationship between female reproductive factors and open-angle glaucoma risk. By limiting the search to the last fifteen years (2010–2025), this review provides recent advances in hormonal epidemiology especially estrogen-specific mechanism for glaucoma. This review also includes studies of diverse populations (Asian, African American, Caucasian) improving generalization of the findings.

Limitation of this study is the high heterogenity and relatively small number of eligible studies. Included studies differed in design (cross-sectional, retrospective, and randomized controlled trials), study populations (Asian, Caucasian, and African American), and outcome measurements, thus preventing quantitative meta-analysis. Future large-scale, well-controlled prospective studies are needed to confirm these associations and clarify the underlying hormonal mechanisms linking female reproductive history to glaucoma pathogenesis.

Acknowledgment

None.

Conflict of Interest

The authors declare no conflict of interest.

Funding

All authors have no conflict of interest.

Author Contribution

ACVG: literature screening, translating, conceptualizing, writing; BK: reviewing, editing; FA: literature screening, translating, editing.

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