

Gender Difference in Ocular Diseases, Risk Factors and Management with Specific Reference to Role of Sex Steroid Hormones

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ABSTRACT

Our eyes are windows to the world and to our soul. The approach to them offers an incredible space for conducting research to learn more about gender differences in ocular health and disease. There is inadequate data about gender differences to accurately plan and implement strategies to address the gender disparities. In this article, we discuss several conditions with ocular manifestations, focusing on those that disproportionately affect women more, with a specific emphasis on the role of sex hormones and the management of the conditions. Articles in the past two and a half decades were selected for this mini-review from the MEDLINE/PubMed database. The search terms used were: “Age Related Macular Degeneration,” “Blindness,” “Cataract,” “Diabetic Retinopathy,” “Dry Eye,” “Glaucoma,” “Ocular Diseases.” To restrict the articles found, we limited search results with the terms: “Estrogen,” “Gender difference,” “Hormone,” “Menopause,” “Sex Steroid Hormones.”

KEYWORDS: Age-related macular degeneration, blindness, cataract, diabetic retinopathy, dry eye, estrogen, gender difference, glaucoma, hormone, menopause-related ocular pathology, menopause, ocular diseases, ocular health in women, prevalence, sex steroid hormones

INTRODUCTION

The worldwide prevalence of moderate-to-severe visual impairment and blindness is 285 million, with 65% visually impaired and 82% of all blind people being 50 years and older. Meta-analysis has shown that two out of three blind people are women, in both developed and developing countries.^[1]

Most of the clinical-based literature affirms that a significant majority of ocular diseases affect women disproportionately compared to men, but that published knowledge mostly describes prevalence.

Eye-health disparities are prevalent for women due to a multitude of causes, some of which are known and some of which remain to be determined. Disparities arise from a range of influences that are biological, behavioral/perceptual, cultural, and societal.

Although sex and gender-based differences appear throughout the lifespan of males and females, the focus of this mini-review will be on adult women. Sex differences in physiology and pathology affecting the

eye fall generally into two categories: Those related to the reproductive system (mostly from the effect of hormones and hormone-based signaling pathways) and those unrelated to the reproductive system. Ocular disorders in women fall into both categories, with disparities prevalent for each.

However, we do not know enough about the etiology of the two categories of eye diseases and their disparities to be able to discuss them separately. More research is needed to understand how hormonal and nonhormonal attributes contribute to eye diseases in women and men, as well as how these influences likely interact in complex ways.^[2]

Hormones are the main regulators of the body’s physiology and affect organ and tissue behavior

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in two ways, directly acting through cell receptors and modulating cell function or indirectly through regulation of metabolism. Most of the ocular tissues have sex steroid hormone (SSH) receptors and respond to the direct regulation of these hormones. The current study examines how hormones are responsible for ocular diseases such as dry eye syndrome, cataract, glaucoma, diabetic retinopathy, and age-related macular degeneration. Women are also more likely to have untreated refractive errors, including nearsightedness, farsightedness, and astigmatism [Figure 1].^[3]

LITERATURE SEARCH

We searched the MEDLINE/PubMed database for articles from January 1997 to October 2021 using the following search terms: “Age-Related Macular Degeneration,” “Blindness,” “Cataract,” “Diabetic Retinopathy,” “Dry Eye,” “Glaucoma,” “Ocular Diseases.” To restrict the articles found, we limited search with the terms “Estrogen,” “Gender difference,” “Hormone,” “Menopause,” “SSH.” Articles with relevant abstracts to this mini-review were retrieved from the search results.

DRY EYE SYNDROME

Dry eye affects twice as many women as men over 50 years of age.^[2]

Dry eye syndrome occurs when eyes do not produce enough tears or the tears are of poor quality and evaporate quickly. It occurs in thyroid eye disease, rheumatoid arthritis, and connective tissue diseases. Dry eye syndrome is most likely related to an imbalance of SSHs associated with advanced age mainly menopause.^[4]

Dry eye has many causes, several of which are unique to women. A large-scale study found that women are

diagnosed with dry eye 6 years earlier, on average than men, leading to significant disability as a chronic condition. This data also showed that women reported higher levels of dry eye symptoms, greater use of dry eye treatment and a greater adverse impact on quality of life [Figure 2].^[2]

We also know that females with premature ovarian insufficiency, a condition phenotypically similar to postmenopause but affecting much younger females are more likely to exhibit ocular surface damage and dry eye symptoms. These effects appear to be independent of tear production, but the mechanisms are still poorly understood.^[2]

CATARACT

Cataract is the leading cause of blindness worldwide for both sexes, with age being the biggest risk factor. In a study, the prevalence of only unoperated cataract in people aged ≥ 60 was estimated to be 58% in north India and 53% in south India. The prevalence of unoperated cataracts increases with age and is higher in women as compared to men (odds ratio 1:8). Women had higher rates of cataract, which was not explained by the difference in access to surgery.^[5]

The proposed pathogenesis for cataracts has been genetic factors and oxidative stress. Laboratory and epidemiologic studies suggest that estrogen in women may confer antioxidative protection against cataractogenesis, but the withdrawal effect of estrogen during menopause leads to increased risk of cataracts.^[1]

Early menarche/late menopause in women has been noted to be beneficial. Some studies have reported protection from contraceptive pills/hormone replacement therapy (HRT). While some have shown no effect/increased risk by HRT. There is no association of cataractogenesis with reproductive span.^[1]

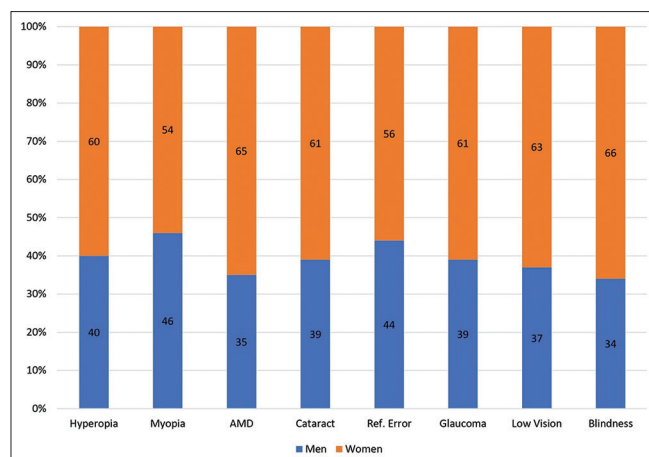


Figure 1: Women in USA have a higher incidence of all major vision abnormalities. Ref. Error– Refractive Error

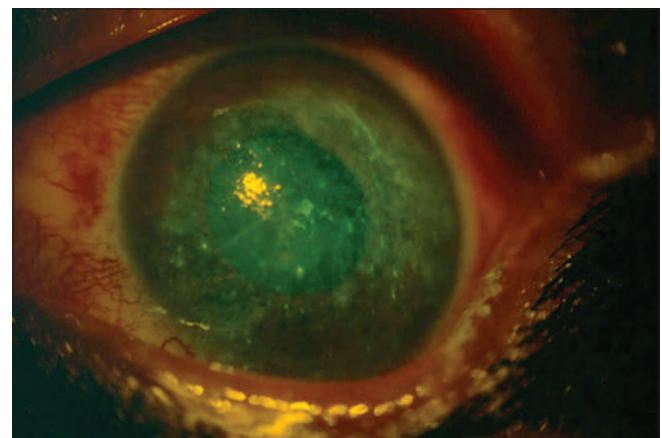


Figure 2: Fluorescein staining of the cornea and conjunctiva of a woman with Dry Eye Disease

GLAUCOMA

Glaucoma is a neurodegenerative disease affecting the retinal ganglion cells, leading to thinning of the retinal nerve fiber layer and changes to the optic disc. Consequently, the patient will experience a progressive visual field loss that may eventually result in blindness. The intraocular pressure (IOP) is commonly elevated in glaucoma, but high IOP is not required for diagnosis. There is no curative therapy for glaucoma, but progression can be prevented or delayed by lowering the IOP, something that can be achieved pharmacologically, surgically or by laser treatment.

Glaucoma, the leading cause of irreversible blindness worldwide, currently affects more than 60.5 million persons worldwide.^[6] The estimated prevalence for India was 11.9 million,^[7] this number has been projected to have increased since then. A meta-analysis estimated the average prevalence of blindness due to glaucoma is 4.5 million (0.5 million to 15.4 million), with an overall predisposition towards men.^[8]

The male:Female ratio differs between various subtypes of glaucoma.^[9] The two main types of glaucoma are primarily defined by the anatomy of the anterior chamber and the chamber angle in the eyes. Angle-closure glaucoma (ACG), is the second-most common glaucoma, which accounts for 26% of all glaucoma worldwide. It is more prevalent in women and in Asian populations.^[6] The prevalence of ACG in the Indian population over 40 years of age is reported to be around 1.26%–1.5%.^[9,10]

The most probable cause of the increased risk of ACG in women is aging and anatomical factors, with women having shorter eyes, cataract, and a shallower anterior chamber leading to limited space in the chamber angle and causing dysfunctional outflow of aqueous humor.^[9,11-14]

In relation to the role of hormones in glaucoma, estrogen receptors are present in the ciliary epithelium and seem to be involved in regulating intraocular pressure and therefore might play a role in glaucoma.^[15] Research has suggested a protective role of estrogen in glaucoma. A longer reproductive period (early menarche and/or late menopause) was associated with decreased risk of Open Angle Glaucoma.^[16,17] Furthermore, the Rotterdam study^[18] showed that early menopause was associated with a higher prevalence of glaucoma. Although the protective mechanism of estrogen against glaucoma is not known, a couple of studies have shown that IOP decreases during pregnancy and increases after menopause, indicating a possible role of estrogen in IOP-regulation.^[19,20] However, one investigation reported

lower prevalence of retinal nerve fiber layer defects in women who received HRT, although the data on the effect of postmenopausal HRT on IOP is mixed.^[21,22] Another study found the use of contraceptive pills for extended periods (≥ 5 years) was associated with an increased risk of glaucoma.^[23] In addition, estrogen has also been found to confer neuroprotection,^[24] which could be important in preventing the death of retinal ganglion cells.

There is evidence that progesterone seems to have the properties of a glucocorticoid antagonist in the eyes. While endogenous glucocorticoids are known to elevate IOP, progesterone may inhibit this effect by competing for the receptor binding site. These receptors have been located in human trabecular meshwork cells, binding both glucocorticoids and progesterone.^[18]

PRIMARY VASCULAR DYSREGULATION SYNDROME

Vascular dysregulation refers to the regulation of blood flow that is not adapted to the needs of the respective tissue. Primary vascular dysregulation (PVD, formerly called vasospastic syndrome) is distinguished from secondary vascular dysregulation based on having no known underlying cause. The prevalence of PVD is much higher in women than in men.^[25]

PVD patients usually have cold extremities, low blood pressure, decreased feeling of thirst, altered drug sensitivity, increased pain sensitivity, prolonged sleep onset time, signs of oxidative stress, low body mass index and often diffuse and fluctuating visual field defects. Cold, emotional or mechanical stress, and starving can provoke symptoms. Nearly all organs, specifically the eye, may be involved. Retinal vessels are stiffer and more irregular and both neurovascular coupling and autoregulation capacity are reduced while retinal venous pressure is often increased in patients with PVD. This condition is associated with an increased risk of other ocular conditions such as normal-tension glaucoma, optic nerve compartment syndrome, central serous choroidopathy, Susac syndrome, retinal artery and vein occlusions, and anterior ischemic neuropathy without atherosclerosis. Furthermore, there is a higher prevalence of optic disc hemorrhages.^[26]

The syndrome manifests at, or shortly after puberty and mitigates or may even disappear with old age, particularly in females after menopause. The symptoms can recur if females receive estrogen replacement therapy after menopause, suggesting estrogen most likely plays a role as well.^[26]

AGE RELATED MACULAR DEGENERATION

Age related Macular Degeneration (AMD) is commonly divided into two types, either as dry, accounting for 80% of all AMD cases, or wet, accounting for the remainder. The dry form is characterized by atrophy of the retinal pigment epithelium underlying the sensory retina, leading to the deterioration of the photoreceptors, whereas the wet form is caused by the growth of pathologic blood vessels from the choroid into the subretinal space, resulting in edema, hemorrhages and in the final stages discoid fibrosis in the central part of the macula.^[27] Although dry AMD is the most prevalent form, the wet type is responsible for most of the severe visual impairment or blindness in AMD.

It was estimated that by 2020, the number of people with AMD globally would be around 200 million and projected to increase to nearly 300 million by 2040. AMD accounts for 8.7% of total blindness globally.^[28]

The most important risk factor for AMD in females is age. Women, in general, have greater life expectancy than men, which could explain the higher incidence of AMD in females.^[29,30] However, a recent meta-analysis reported no sex difference in AMD.^[7]

Apart from aging, other risk factors for AMD are heredity, ethnicity (higher risk in white people), smoking, diet, obesity, hyperopia, and the presence of lens opacities. Smoking is the biggest modifiable risk factor for AMD. Other factors with less convincing evidence for their influence on AMD risk include cardiovascular factors, sunlight exposure, iris color, and alcohol consumption.^[29,30]

Estrogen exposure (endogenous or exogenous) shows mixed results. Early menarche and/or late menopause, i.e., a long reproductive period in a woman, as well as a longer duration of lactation was associated with lower risk of AMD in some studies like the Blue Mountain Eye Study. The protective effects of oral contraceptives, HRT have been demonstrated. Yet, other reports have failed to show the above-mentioned effects.^[1]

Oxidative stress, chronic inflammation, and angiogenesis are suspected to be involved in the pathogenesis.^[27,31,32] The anti-oxidative property of estrogen and its withdrawal effect at menopause forms the basis of the oxidative stress mechanism.^[31,33] Several studies have shown a significant comorbidity between AMD and cataracts, suggesting common pathogenic pathways.^[34,35] In contrast to cataracts, however, AMD is also characterized by chronic low-grade inflammation.^[33] The anti-inflammatory properties of estrogen and its ability to regulate several signaling

pathways are other mechanisms that have been implied in AMD pathogenesis.^[33]

One study explored the role of dehydroepiandrosterone sulfate (DHEAS) in AMD and found an inverse correlation between AMD severity and DHEAS serum levels.^[36] DHEAS is a precursor for estrogen and testosterone, and since AMD usually occurs after menopause, it may be assumed DHEAS may be playing a role. However, in a more recent study, no association between the serum DHEAS concentration and exudative AMD was established.^[37]

DIABETIC RETINOPATHY

Diabetic retinopathy accounts for around 1% of all visual impairment globally.^[38] Although it is a smaller contributor, there appears to be an upward trend in the prevalence as a result of an increase in the number of diabetics and longer life spans. It is also the leading cause of preventable blindness in people of working age, having a huge economic impact on society.^[39] About 22.3% of all diabetic patients, regardless of type, develop diabetic retinopathy, which is one of the most common complications of diabetes.^[38]

Diabetic retinopathy is a microvascular disorder of diabetes, which may be classified as either non-proliferative or proliferative. The latter is a more severe condition where abnormal blood vessels develop in the retina, leading to leakage, vitreous hemorrhage, and eventually fibrotic strands formed from the retina into the vitreous with a risk of retinal detachment. In addition, diabetes may also result in macular edema.

Recent reviews found that in majority, there was an insignificant gender difference in regards to diabetic retinopathy while some reported a higher predisposition for males.^[1,40,41] In addition, a recent Japanese study has reported that women with type 2 diabetes mellitus have a higher predisposition for advanced diabetic retinopathy at baseline and that the female sex is an independent risk factor for the progression of diabetic retinopathy.^[42]

The differences in findings regarding gender distribution indicate that other risk factors than gender are also in play in its pathogenesis. Some studies showing decreased risk of developing diabetes in menopausal women taking exogenous estrogen (HRT) indicating a possible role of SSHs.^[43,44] In addition, the worsening of retinopathy during pregnancy, especially in diabetes type 1, is well established.^[45] In view of the above, the diabetic retinopathy risk is lower in women following a tight metabolic control regimen during pregnancy. The risk often increases again in the postpartum period since the tight regimen is no longer followed. The basis for

possible gender-based effects, estrogen-related or not, in pathogenesis are unknown at present.

A study in retinal pigment epithelium cell cultures found increased production of vascular endothelial growth factors (VEGF) when exposed to a higher concentration of progesterone. This could explain the reason why VEGF has been identified to be closely related to the development and progression of diabetic retinopathy.^[46]

In addition, a few investigations also point towards an increased risk of retinal vein occlusion and retinal artery occlusion in women taking oral contraceptives.^[46]

GENERAL RISK FACTORS FOR OCULAR DISEASES IN WOMEN

1. Lack of awareness for regular checkups after the age of 40 years
2. Early menopause (E.g., surgically induced at an early age)
3. Malnutrition from childhood
4. Hormonal imbalance
5. Inappropriate drug usage causing ocular side effects
6. Hormonal changes after menopause increases the risk
7. Environmental exposure such as smoke and dry air etc.

PREVENTION

Lifestyle changes like unhealthy diet, lack of exercise, smoking, etc., are all contributing factors affecting overall eye health. Smoking increases the risk of cataracts and AMD. Women must preserve eye health by taking diet rich in Vitamin A, C, E, omega 3 fatty acids, and zinc. Limiting alcohol intake, especially for dry eyes and decreasing sunlight exposure is also beneficial.

Estrogen seems to have a protective effect potentially via its vasodilator effects. Hormonal therapy in post-menopausal women might be protective against AMD and glaucoma. Estrogen is considered to have a prophylactic effect against eye diseases [Table 1]. However, it does not always exert a prophylactic effect as adverse events, such as thrombosis, may occur. There

is insufficient evidence to recommend hormone therapy for the prevention of ocular disease. Thus, caution should be exercised in hormonal therapy.

CONCLUSION

There are other conditions which also have a higher prevalence among women but there is no clear role of SSHs, such as refractive errors, Fuchs endothelial cell dystrophy, migraine, thyroid eye disease, trachoma, uveitis, and autoimmune disease associations.

At present, the evidence base to guide sex and gender-based medicine is insufficient. Further studies on the role of gender and hormones in ocular disorders, ocular blood flow, and its regulation are needed to help expand our understanding.

In summary, there is evidence that gender differences exist with regard to the incidence of ocular disease. Sex hormones are one of the causes in the difference of prevalence of some ocular diseases between the two sexes.

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Conflicts of interest

There are no conflicts of interest.

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Table 1: Prevalence of ocular pathologies by gender

Ocular pathologies more common in females	Ocular pathologies more common in males
1. Dry eye syndrome	1. Inherited and genetic stargardt's disease (macular degeneration)
2. Cataract	2. Color blindness
3. Age related macular degeneration	3. Retinitis pigmentosa
4. Glaucoma	4. Acquired central serous retinopathy
5. Autoimmune diseases	5. Diabetic retinopathy

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