Review Article

Retinal changes in preeclampsia

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ABSTRACT

Background: The eye undergoes a series of physiological changes during pregnancy in response to metabolic and hormonal adaptation. Preeclampsia (PE) is the main cause of maternal morbidity and is associated with serious pregnancy-related complications. Characterized by hypertension and proteinuria, PE affects 2–8% of pregnancies globally. Previous studies have indicated that PE compromises retinal health. We examined the effects of PE on retinal structure and vasculature.

Methods: We conducted a literature review by searching PubMed/MEDLINE, Embase, and Scopus using terms pertaining to PE and the retina. The review included articles published between January 1, 1990, and May 30, 2024. The articles were selected based on their relevance to the topic. The key findings are summarized to offer a comprehensive overview of current knowledge, highlight the pathophysiology and manifestations of PE-related retinal changes, and propose clinical implications, diagnostic clues, and management strategies.

Results: PE is associated with visual disturbances caused by various retinal changes, including arteriolar narrowing, vasospasm, hemorrhages, exudates, serous retinal detachment, macular edema, retinal vein occlusion, and choroidal ischemia. These are mostly evident on fundus examination and frequently resolve postpartum. The underlying pathophysiology involves endothelial dysfunction, hypertension, inflammation, and coagulopathy. These retinal changes have important clinical implications and may warrant early detection, prompt multidisciplinary management, and close follow-up. Although most PE-associated retinal disturbances spontaneously resolve after the termination of pregnancy, approximately one-third of patients have been reported to experience long-lasting ocular consequences.

Conclusions: Visual disturbances may be an early clinical manifestation of PE. Early detection and prompt management may help reduce fetal and maternal morbidity and mortality. Understanding the underlying pathophysiology of PE-related retinal manifestations is crucial for optimal management, because the majority of manifestations are reversible. Although retinal changes secondary to PE typically resolves postpartum, some studies have suggested that women with PE may have a higher long-standing risk of ocular disorders. A multidisciplinary team approach involving obstetricians, ophthalmologists, and healthcare providers is essential for the immediate and long-term management of ocular consequences in pregnancy. Consequently, additional studies associated with robust methodologies are required to develop clinical guidelines.

KEYWORDS

preeclampsia, retina, pregnancies, hypertensive retinopathies, retinal detachments, machine learning, artificial intelligence, maternal health, retinal hemorrhages, postpartum

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INTRODUCTION

Multiple organs of the pregnant women are involved during pregnancy to provide an appropriate environment for embryo development and to prepare the mother for delivery [1]. For example, the cardiovascular, respiratory, gastrointestinal, hematologic, and visual systems are influenced throughout pregnancy [2-4]. Although these alterations during pregnancy are often normal, 5–20% of pregnancies are associated with pathological events [5].

The ocular system undergoes a series of physiological modifications during pregnancy in response to metabolic and hormonal adaptations [4, 6]. These include an increase in eyelid pigmentation, melasma, dry eye disease, changes in corneal thickness and curvature, myopic shift, and reduction in visual field [4, 7, 8]. However, a spectrum of pregnancy-induced etiologies can lead to pathological vision changes [9]. Numerous maternal vision disorders are attributable to the progression of pre-existing ocular impairments such as diabetic retinopathy and glaucoma [10, 11].

Nevertheless, other categories of ophthalmic impairments are believed to develop *de novo* during gestation. For example, systemic diseases such as disseminated intravascular coagulation (DIC), which may occur more frequently during pregnancy, can lead to ocular abnormalities. Moreover, pregnancy complications such as preeclampsia (PE) might cause ophthalmic pathologies leading to visual disturbances [8, 9, 12].

PE is one of the most common maternal health concerns, affecting 2–8% of pregnant women worldwide, and is responsible for approximately 500 000 fetal deaths and 46 000 maternal deaths globally per year [13-15]. PE is a hypertensive disorder of pregnancy, defined as the *de novo* onset of hypertension after the 20th week of gestation, accompanied by proteinuria, with or without end-organ damage, such as serous retinal detachment, acute kidney injury, thrombocytopenia, hemolysis, and liver or neurological disturbances [14-17].

The retina does not undergo any particular modification during normal pregnancy. However, this complex ocular structure is frequently impaired or damaged in pregnant women with PE [17, 18]. It is composed of neural tissue and supporting cells located in the posterior segment of the eye. The retina plays a notable role in processing the visual information received and conveying signals to the brain through the optic nerve [19, 20]. Owing to its high metabolic activity and oxygen demand, the retina possesses unique vasculature that supplies its requirements while maintaining transparency for light transmission [19]. The hypertensive component of PE can induce vasoconstriction in the retinal vasculature with subsequent vascular narrowing [21]. As retinal function relies on intact vasculature and adequate blood perfusion, disruptions caused by this hypertensive disorder can precipitate various pathologies that manifest as visual symptoms [17, 18]. We aimed to synthesize and classify the existing body of knowledge pertaining to the pathophysiology, diagnosis, and management of PE-induced retinal disorders. To achieve this objective, we conducted an in-depth review of the pertinent literature spanning three decades of research.

METHODS

For this narrative review, we explored the effects of PE on the retina through a literature search spanning 34 years using electronic databases, including PubMed/MEDLINE, EMBASE, and Scopus. The keywords used in the search strategy included "preeclampsia," "hypertensive disorders of pregnancy," "retinal health," "retinal vasculature," "retinopathy," "hemorrhage," "retinal detachment," "macular edema," "choroidal ischemia," and "treatment." The search was limited to articles published from January 1, 1990, to May 30, 2024, and included narrative reviews, systematic reviews, original research articles, case reports, and observational studies. The selected articles were assessed based on their relevance to the impact of PE on retinal structure and function, including retinal vascular changes, pathological findings, diagnostic methodologies, and therapeutic interventions. This narrative synthesis integrates the findings of diverse studies to provide a comprehensive overview of current information and the knowledge gaps in the field of PE-related retinal complications.

RESULTS and DISCUSSION

Retinal changes attributable to PE

PE can lead to various systemic complications, including those affecting the eyes. The retinal changes observed in PE are mainly attributable to alterations in the microcirculation caused by hypertension and endothelial dysfunction [18]. These changes can be identified through ophthalmological examination [4] and may include the following:

Arteriolar narrowing and vasospasm: Among the retinal changes that occur during PE, vasospasm can play a critical role in subsequent events. Vasospasm and arteriolar narrowing can be observed in the choroidal arterioles and central retinal or posterior ciliary arteries [22]. Arteriolar narrowing is the primary response of retinal vasculature to systemic arterial hypertension during PE [23]. Narrowing of the choroidal arterioles can ultimately lead to choroidal ischemia, resulting in increased vascular permeability. Consequently, fluid accumulation between the neurosensory retina and the retinal pigment epithelium causes retinal detachment [24]. Moreover, arteriolar narrowing is the most common finding on fundus examination among women with PE [25, 26].

Hemorrhage: Retinal hemorrhage is an important sign of systemic vascular disease. Etiologies of this condition comprise a vast array of diagnoses. However, diagnostic clues can help to differentiate between these conditions. PE is an urgent obstetric condition and an important cause of retinal hemorrhage. During PE, intraretinal hemorrhage, Elschnig's spots caused by choroidal ischemia, and serous retinal detachment can be observed [23, 27, 28]. These events typically occur bilaterally and vary in intensity. Furthermore, Roth's spots have also been reported in preeclamptic retinal hemorrhage [28].

Exudates: The presence of retinal hard exudates is an important sign of an underlying systemic disease involving the retina. Among these diseases, diabetes mellitus, hypertension, and PE should be considered [21, 29]. Retinal hard exudates are composed of lipid and proteinaceous material. These exudates occur because of leakage caused by an impaired blood–retinal barrier. Among other conditions, PE is one cause of this impairment [30].

Serous retinal detachment: Serous retinal detachment is a rare cause of vision loss during pregnancy, occurring in less than 1% of preeclamptic cases [31]. However, the incidence of this complication increases in the more harmful variant of PE known as "hemolysis, elevated liver enzyme levels, and low platelet levels" (HELLP) syndrome [32]. Choroidal ischemia occurs because of vasospasm, leading to subretinal leakage and retinal detachment [33]. This condition is usually bilateral, diagnosed after childbirth, and associated with primipara and/or cesarean delivery [34]. Surgical intervention is not appropriate for managing this condition because optimal treatment focuses on addressing the underlying cause. In the context of PE, management involves stabilization and expedited fetal delivery [17, 31]. Fortunately, this condition usually resolves and rarely causes permanent vision loss [17, 33].

Macular edema: Macular edema is caused by fluid accumulation in the macula and central retina, which are responsible for sharp central vision. The macular accumulation of fluid results from an imbalance between the mechanisms that regulate retinal fluid influx and efflux. This condition can have various etiologies, including diabetes mellitus, age-related macular degeneration, retinal vein occlusion, and PE [35]. During PE, fundoscopy commonly reveals macular edema, which is often concurrent with serous retinal detachment and other retinal alterations [36]. Similar to retinal detachment, macular edema typically requires several weeks to resolve; however, periocular corticosteroid administration has been reported to accelerate resolution in selected cases [37].

Retinal vein occlusion: During pregnancy, the risk of thromboembolism increases, with greater likelihood in the third trimester and the postpartum period. This hypercoagulable state may induce retinal vein occlusion even in normal pregnancy [38]. By contrast, PE—and its fulminant form, HELLP syndrome—can cause retinal vein occlusion [39]. HELLP syndrome is a thrombotic microangiopathic vasculopathy that can lead to coagulation in different parts of the vascular system, and in this context, can cause central retinal vein occlusion. Retinal vein occlusion secondary to PE is expected to occur during the postpartum period [39].

Choroidal ischemia and infarction: Mild arteriolar spasm in the bulbar conjunctival vessels is considered normal in typical pregnancies [40]. However, in PE, choroidal ischemia—and in severe cases, choroidal infarction—typically arises from pronounced arteriolar vasospasm. Serous retinal detachment may also result from choroidal ischemia [34]. In addition to retinal detachment, yellowish, opaque retinal pigment epithelial lesions, also known as Elschnig's spots, have been mentioned as a manifestation of choroidal ischemia [41].

Pathophysiology

Endothelial dysfunction: PE initially leads to systemic endothelial dysfunction, which is central to its pathophysiology. During the early stages of pregnancy, PE begins with the aberrant invasion of trophoblasts during placenta formation, resulting in oxidative stress and reduced blood flow to the uterus and placenta [42]. This process increases production of anti-angiogenic factors, such as soluble fms-like tyrosine kinase 1 (sFlt-1) and soluble endoglin, and reduced production of placental growth factor, inducing an imbalance between pro- and anti-angiogenic factors [42, 43]. Increased concentrations of sFlt-1 counteract the effects of vascular endothelial growth factor (VEGF), resulting in endothelial cell damage and impaired vascular healing mechanisms [42]. Increased VEGF levels stimulate the release of nitric oxide (NO) by increasing the expression of NO synthase in endothelial cells [21, 44]. This activates endothelial cells, causing changes in capillary structure and a decrease in NO levels [45]. NO stimulates the activation of soluble guanylate cyclase, which in turn triggers the creation of cyclic guanosine monophosphate (cGMP) [46]. Additionally, in PE, the balance between vasoconstrictive and vasodilatory prostaglandins is disrupted, leading to reduced levels of prostaglandin I2 [47, 48]. Prostaglandin I2 stimulates adenylyl cyclase and enhances the production of cyclic adenosine monophosphate (cAMP). Both cGMP and cAMP reduce the levels of calcium within cells, resulting in the relaxation of smooth muscle and subsequent vasodilation [49-51]. Therefore, endothelial dysfunction results in notable alterations in retinal structure and function, including thickening of the capillary basement membrane, loss of perivascular cells, impairment of the blood–retinal barrier, and neovascularization [52].

Hypertension: Hypertensive retinopathy refers to the retinal vascular alterations caused by high systemic blood pressure. In the early stages, vasospasm and elevated vascular tone cause generalized narrowing of the retinal arterioles and arteries. This response to elevated blood pressure results in localized or widespread constriction of blood vessels. Furthermore, vascular leakage is caused by elevated blood vessel permeability [53]. The resultant retinal changes include a reduction in the retinal artery-to-vein ratio and the presence of cotton wool spots, Elschnig's spots, and serous retinal detachments [43, 54, 55]. In chronic hypertension, structural changes are evident in the vessel wall, including thickening of the inner layer and degradation of hyaline [56]. Microaneurysms may also develop under these circumstances. Cotton wool spots are ischemic foci in the retinal nerve fiber layer caused by severe hypertension [56]. Severe hypertension can lead to elevated intracranial pressure, compromised optic nerve blood supply, and severe bilateral optic disc swelling [45].

Coagulopathy: The hypercoagulable state caused by PE also exacerbates retinal damage. Elevated concentrations of pro-coagulant substances and reduced thrombolysis lead to the development of microthrombi within the retinal blood vessels. Microthrombi can induce retinal ischemia and infarction [55], resulting in retinal damage manifesting as cotton wool spots and retinal hemorrhages [36]. Pregnancy-related hypercoagulable states may arise because of the increased production of thrombin and procoagulant factors, with reduced levels of endogenous anticoagulants such as protein C, protein S, and antithrombin III [57].

Furthermore, individuals with PE exhibit increased levels of tissue factor, factor VIII, von Willebrand factor antigen, and fibrinopeptides A and B [21, 51, 58].

Inflammation: PE contributes to retinal injury through the activation of various inflammatory factors. Elevated levels of cytokines, such as interleukin-6 and tumor necrosis factor-alpha, lead to increased vascular permeability and leukocyte adhesion to the endothelium, exacerbating endothelial damage and retinal manifestations, including hemorrhages and exudates [59, 60]. Oxidative stress is crucial in the development of PE and affects the retina. The imbalance between pro- and antioxidant systems leads to the build-up of reactive oxygen species, which directly damage retinal cells and exacerbate endothelial dysfunction. Additionally, oxidative stress stimulates inflammation, thereby exacerbating vascular injury and causing retinal damage [43, 61]. Figure 1 summarizes the retinal changes associated with PE and their underlying pathophysiological mechanisms, providing a clear overview of the relationships between these conditions.

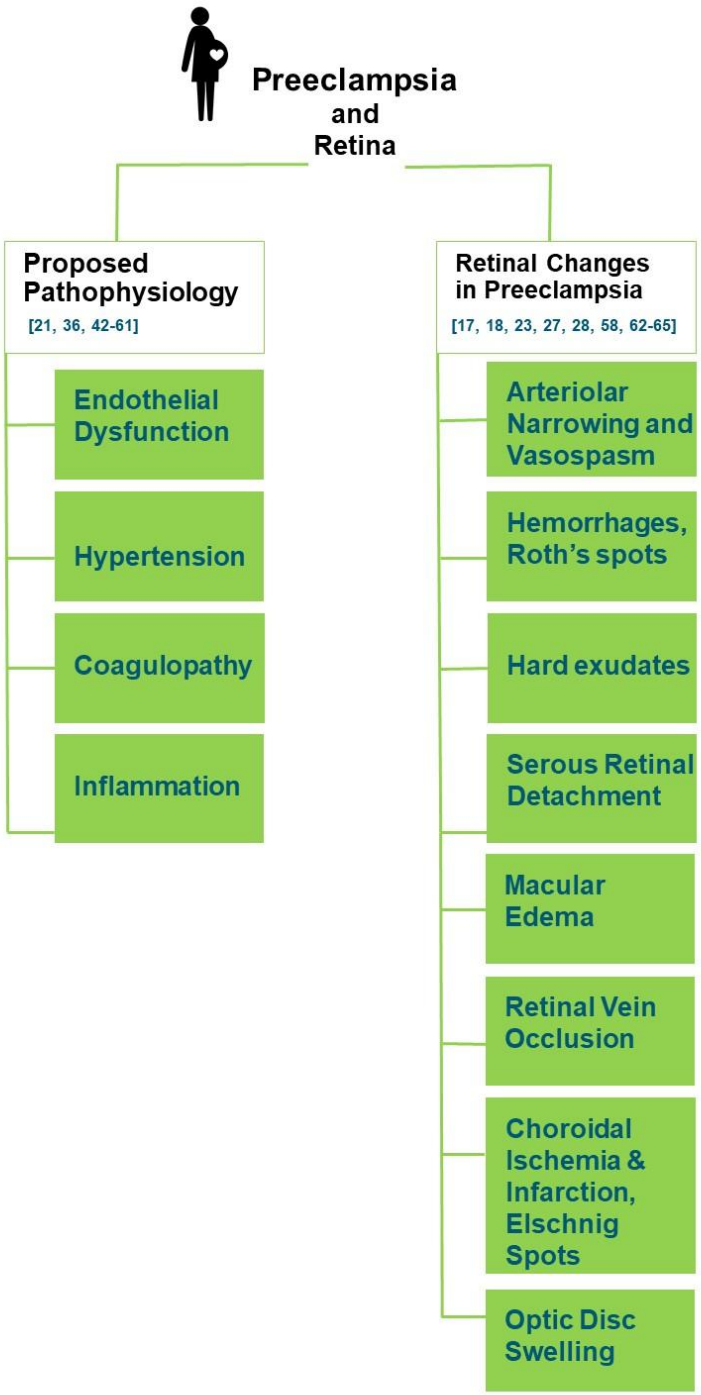

Figure 1. Retinal changes and pathophysiological mechanisms in preeclampsia

Clinical implications and diagnosis

PE can cause retinal damage, resulting in a spectrum of visual complaints that correlate with the severity of retinal injury. Visual symptoms have been reported in approximately 40% of women with severe PE [36]. Patients with PE commonly have a range of ocular symptoms, including photopsia, blurred vision, color vision changes, blindness, visual field abnormalities, serous retinal detachment, and cortical blindness [21, 66]. Blurred vision is a prevalent symptom that can arise from retinal edema, ischemia, or hemorrhages [21, 67]. Cortical blindness is a severe and alarming consequence of PE that may resolve following the end of pregnancy, often resolving within several days, although recovery times may vary. It can also occur because of vasospasm and increased permeability of blood vessels of the brain [21, 58]. Neuroimaging may reveal a range of findings in the occipital lobes [58].

Photopsia is a sudden visual disturbance manifesting as flashes of light in the field of vision, commonly attributable to retinal detachment [68]. Serous retinal detachment occurs when the neurosensory retina separates from the retinal pigment epithelium, leading to vision impairment in patients with PE. Although it can manifest at any time during pregnancy, it typically occurs just before or shortly after childbirth. Bullous and bilateral detachment are common manifestations [69], with most patients experiencing sudden vision loss. Patients with the most severe types of PE exhibit the most unfavorable fundoscopic manifestations. Some studies have indicated an unfavorable fetal prognosis, whereas others have found no prognostic consequences for the fetus [21, 23].

The diagnosis of hypertensive retinopathy requires a thorough ophthalmic examination, including fundus photography [70], B-scan ultrasonography [71], and optical coherence tomography (OCT) [72]. These diagnostic tools can be used effectively in pregnant women. These noninvasive modalities are crucial for assessing retinal injuries, optic nerve changes, and choroidal abnormalities. Typically, invasive procedures, such as fundus fluorescein angiography, are avoided because of uncertainty regarding their teratogenic effects [36, 73]. Fundus photography captures high-resolution images of the retina, allowing documentation of hypertensive retinal alterations [70, 74]. OCT is another valuable tool for evaluating retinal thickness and identifying macular edema, which can develop in severe cases of hypertensive retinopathy [72]. OCT angiography facilitates detailed blood vessel image acquisition in different retinal layers, providing a three-dimensional representation of the vascular layers [62, 67]. Furthermore, a grading system designated as the Keith–Wagener–Barker classification is employed to evaluate the severity of hypertensive retinopathy. This approach classifies hypertensive retinopathy into four grades based on the severity of retinal arteriolar alterations, hemorrhages, exudates, and optic disc swelling [54, 75].

Management

Although most PE-associated retinal disturbances spontaneously resolve after pregnancy, approximately one-third of patients have been reported to experience long-lasting ocular consequences [17, 18].

The first step in managing the ocular complications of PE is elimination of the underlying cause [21]. Delivery is the primary treatment modality for PE. The termination of gestation reverses most ophthalmic disturbances [17, 32, 76]. However, several existing complementary remedies restrict the progression of PE to eclampsia and prevent further sequelae [76].

Elevated blood pressure associated with PE requires the administration of antihypertensive medications [77]. The American College of Obstetricians and Gynecologists (ACOG) recommends lowering the blood pressure to less than 160/110 mmHg [78]. Because of contraindications and other concerns of medication use during pregnancy, the choice of antihypertensive agents is limited. Labetalol, hydralazine, methyldopa, beta-blockers, nifedipine, diazoxide, and nitroprusside are currently administered to control hypertension [76, 77]. Methyldopa remains one of the commonly used antihypertensive medications during pregnancy [79]. Labetalol can be administered orally or intravenously [77]. Other medications are used less frequently as monotherapy or in combination regimens [76, 78].

The second most notable agent in PE treatment is magnesium sulfate [17, 79]. This neuroprotective substance prevents the progression of PE to eclampsia [17, 79]. The ACOG exclusively recommends magnesium sulfate administration in severe cases of PE [79]. Studies have also illustrated the effects of nutritional factors and exercise on the control of PE. Aerobic exercise combined with a low-salt, antioxidant-rich diet is beneficial for pregnant women and can prevent and control hypertensive disorders [77].

In addition to general PE management and conservative approaches, some retinal injuries may require specific treatments and interventions. Depending on the retinal pathology, supplemental ophthalmic medications and interventions can be cautiously employed to prioritize the well-being of the mother and fetus [4, 55, 80, 81].

The use of medications during pregnancy is subject to numerous restrictions, as several ophthalmic agents confer potential risks to developing embryos. Notably, acetazolamide and certain subtypes of beta-blockers have been identified as detrimental to the fetus [55, 82, 83]. However, the limited available evidence suggests no teratogenic effects of topical prostaglandin analogs [55, 84]. In the absence of contraindications, preferred ophthalmic agents can be prescribed according to the circumstances and ophthalmologist's diagnosis [55].

Although most cases of retinal injury and detachment recover after delivery, surgery may rarely be required. Surgeries and invasive procedures must be considered only in urgent circumstances, and preferably in the presence of the obstetrical team [55, 81].

Finally, pregnant women experiencing ocular manifestations of PE benefit from the collaboration of a multidisciplinary team comprising primary eye health care providers, ophthalmologists, and gynecologists aimed at optimizing maternal outcomes while highlighting the significance of postpartum follow-up care [4, 8, 85].

This narrative review summarizes key issues concerning PE-related retinal manifestations, pathophysiology, diagnosis, and management, according to studies published over a time span of more than three decades, as a road map for health care providers. However, the lack of a comprehensive systematic search strategy and meta-analysis is a limitation of this study. Further studies focusing on certain ocular manifestations of PE and their long-term consequences, preferably using a meta-analytic approach, could clarify the precise likelihood of visual consequences. In addition, investigating the association between observed ocular changes and maternal/fetal morbidity and mortality could provide additional practical guidance on this topic. Early prediction of PE is vital for controlling disease progression. Recent studies have exploited machine learning and artificial intelligence (AI) in the risk prediction for PE and related subtypes [86]. The use of AI algorithm-based retinal fundus photographs has demonstrated value in predicting PE [87]. Further studies using similar approaches could develop AI-based applications to predict short- and long-term visual outcomes in women who develop PE and its related complications.

CONCLUSIONS

PE, recognized as one of the most prevalent and severe complications of pregnancy, may compromise retinal integrity by disrupting retinal vascular structure and blood perfusion. Investigation of the impact of PE on retinal health has highlighted the critical need for early detection and effective and timely management of this condition throughout gestation. Visual disturbances may represent an early clinical manifestation of PE. Therefore, early detection and prompt management may help reduce fetal and maternal morbidity and mortality. These findings emphasize the associations between PE and diverse retinal manifestations, thereby accentuating the potential long-term implications for maternal visual health. Future efforts should prioritize sustained interdisciplinary collaboration between obstetricians and ophthalmologists to advance our understanding of these connections and to devise targeted interventions aimed at maternal ocular well-being.

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