

Ophthalmic Complications and Ocular Changes in Pregnancy- A Review

Abstract

Pregnancy results in metabolic, hemodynamic, vascular, and immunologic changes. These physiological changes affect multiple organ systems including the visual system. The ophthalmic changes that occur during pregnancy are divided into physiological or pathological. Although ocular changes are common in pregnancy, many are mild, temporary, and require little to no treatment. However, it is important to recognize that serious ophthalmic pathology can occur which requires immediate medical intervention. This article is a review of the pathological and physiological changes which occur within the parturient as well as the safety of medication used to treat various conditions.

Objective: The aim of this study was to review physiologic and pathologic ocular changes that are associated with pregnancy in pregnant women. After reading this article, readers should be able to:

- i. Distinguish physiological pregnancy-related ocular changes from pathological
- ii. Assess the relevance of ocular disease to the choice of childbirth method
- iii. Ophthalmic medication safe for pregnancy

Keywords: Anti-phospholipid Syndrome (APS); Central Serous Chorioretinopathy (CSCR); Diabetic Retinopathy; Disseminated Intravascular Coagulation (DIC); Eye Diseases in Pregnancy; Graves' Disease; Idiopathic Intracranial Hypertension (IIH); Ocular Changes; Ocular complications in Pregnancy; Preeclampsia; Eclampsia, Prolactinoma; Pseudotumor Cerebri; Sheehan's Syndrome; Ophthalmic medication in pregnancy

Abbreviations: CSCR: Central Serous Chorioretinopathy; DIC: Disseminated Intravascular Coagulation

Introduction

Pregnancy is known to cause several physiological changes in the parturient. These physiological changes affect multiple organ systems including the visual system [1,2]. The ophthalmic complications are divided into physiologic and pathologic changes. Pathologic changes in pregnancy are further segregated into three categories including: first time ocular pathology during pregnancy, modification of an existing ocular pathology, and ocular complications of systemic disease [3].

Although ocular complications are common in pregnancy, many are mild, temporary, and require little to no treatment. However, it is important to recognize that serious ophthalmic pathology can occur which requires immediate medical intervention. This article is a review of the pathological and physiological changes which occur within the parturient.

Physiologic changes

Pigmentation of the eyelids and around the eye is commonly increased during gestation. Known as chloasma or melasma, the increased pigmentation usually is reversible and regresses after delivery. Current studies suggest that the elevation of the

hormone melanin in pregnancy results in increased cutaneous melanogenesis and melanocytosis [4].

Pregnancy also affects normal tear film and corneal physiology. Tear production decreases due to lacrimal dysfunction, resulting in dry eye syndrome [5,6]. Also, corneal sensation is significantly decreased [7-9]. The combination of poor tear film and diminished corneal sensation, make contact lens wear difficult and somewhat dangerous. Any symptomatic contact lens wearer during pregnancy should discontinue contact use to prevent more serious complications. Other refractive changes in pregnancy may be due to transient loss of accommodation. A loss of accommodation has been reported with pregnancy and lactation during the postpartum [3]. Pregnancy is also known to alter corneal thickness and curvature [8-10]. Due to these physiological changes, it is better to delay refractive surgery during pregnancy. Refractive corneal procedures such as LASIK are contraindicated and should be postponed until refractive changes stabilize in the postpartum. Also, dry eye and decreased corneal sensation could result in significant postoperative complications such as poor wound healing and corneal melt [11]. It is even recommended to delay changing prescription glasses as new lenses are not likely to be suitable once physiological changes resolve in the postpartum. Intraocular pressure can also be affected. It can be significantly decreased during pregnancy [12-15].

Review Article

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Ocular pathology initially presenting in pregnancy

Ocular pathology can occur secondary to systemic diseases. Certain systemic diseases such as eclampsia, preeclampsia, and Sheehan syndrome are specific to pregnancy while antiphospholipid antibody syndrome (APS), benign intracranial hypertension, Graves' disease, and disseminated intravascular coagulation (DIC) have an increased frequency in pregnancy [11,16].

Preeclampsia: Preeclampsia is the onset of hypertension with either proteinuria or end-organ dysfunction after 20 weeks of gestation in a previously normotensive woman. On the other hand, eclampsia is defined as the development of grand mal seizures in a woman with preeclampsia. However patients may have preeclampsia superimposed upon chronic, preexisting hypertension [17,18].

Funduscopy examination is important with these patients because retinal vascular changes mirror placental vascular changes. Vascular changes of the placenta may permanently affect the fetus. Thus, ophthalmoscopic fundus examination is an important screening tool for both maternal and fetal care. Fundus photography through an undilated pupil may be a helpful tool for evaluating this disease. The visual system, especially the retina, can be substantially affected in preeclampsia/eclampsia patients, resembling an acute form of hypertensive retinopathy [19]. 25% of the patients with preeclampsia and 50% with eclampsia experience visual changes including blurred vision, photopsias (perceived flashes of light), scotomas, diplopia, amaurosis, dyschromatopsia (disorder of color vision), transient bilateral visual loss, and cortical blindness [20,21]. Retinal vascular changes also occur which are very similar to hypertensive retinopathy. These changes may include edema, soft exudates, hemorrhages, nerve fiber layer infarcts, and vitreous hemorrhage secondary to neovascularization. The earliest changes are often focal arteriolar spasm followed by arteriolar attenuation, conditions which resolve after pregnancy [19].

Later changes in the retina include soft exudates and hemorrhages. Severe cases of preeclampsia/eclampsia may present with papilledema, retinal edema, serous exudative retinal detachments, optic atrophy, and acute ischemic optic neuropathy [19]. Retinal changes are correlated with the severity of preeclampsia or eclampsia [22]. Choroidal and optic nerve head changes are also associated with low birth weight and low Apgar scores [23]. Therefore, fundus evaluation in patients with pregnancy induced hypertension is an important procedure to help predict adverse fetal outcomes [24].

However, the most common finding is focal retinal arteriolar narrowing. Yet, studies have shown that the degree of retinopathy is correlated with the severity of preeclampsia/eclampsia within the patient. These retinal hypertensive changes may become exacerbated by underlying microvascular diseases caused by chronic hypertension, diabetes, or renal pathology [19].

As discussed above, serous exudative retinal detachments may occur in severe cases of preeclampsia or eclampsia [25]. It is suggested that the underlying pathophysiology is related to poor choroidal perfusion and the resultant subretinal leakage. Serous exudative retinal detachments present as bullous, bilateral, and

with preeclampsia (hypertensive) retinopathy changes. These changes are reversible with most symptoms resolving weeks after delivery [19,25].

A rare complication that may also be seen in severe case of preeclampsia or eclampsia is cortical blindness. Transient vision loss is hypothesized to be due to cerebral edema. One hypothesis suggests that vasospasm causes transient ischemia, resulting in cytotoxic edema. Once again visual changes are reversible and resolve with the remission of preeclampsia with delivery [26].

Severe retinopathic changes may illicit the need to terminate the pregnancy when fetal or maternal safety is compromised. Severe retinopathy with rapidly progressing arteriospasm denotes a compromise in the maternal circulation [19]. Choroidal and optic nerve head changes are also associated with low birth weight and low Apgar scores [23]. Therefore in order to increase fetal prognosis, caesarian delivery may be indicated. Maternal safety may also be jeopardized by the presence of hypertensive retinopathy in all four quadrants in both eyes. Hypertensive retinopathy due to preeclampsia indicates maternal renal and vascular compromise [19]. A premature termination of pregnancy via caesarian may be considered. However there are no clear guidelines regarding termination of pregnancy due to retinal changes. Constant communication and teamwork must be instilled between the obstetrician and the ophthalmologist.

Multiple Sclerosis: Besides preeclampsia, other important systemic disorders which have ocular involvement include multiple sclerosis and Grave's disease [1,16,27]. Women with multiple sclerosis (MS) who intend to become pregnant should receive Class B medications for MS and its symptoms [28]. Breastfeeding and treatment options after delivery should be discussed with patients for possible resumption of disease-modifying drugs and prevention of postpartum flare-ups [29].

Central Serous Chorioretinopathy: Central Serous Chorioretinopathy (CSCR) can occur during pregnancy with increased frequency during the third trimester. Patients present with visual loss, central scotomas, metamorphopsia, delayed retinal recovery following photostress, loss of color saturation, and contrast sensitivity. CSCR may present with a serous subretinal exudation with an underlying retinal pigment epithelium detachment. The exact mechanism is unknown but is hypothesized to include abnormal ion transport across the retinal pigment epithelium and focal choroidal vasculopathy. Optical Coherence Tomography (OCT) is the diagnostic investigation of choice. Central Serous Chorioretinopathy is reversible after several months of postpartum [30]. However, CSCR is known to recur in the same eye during future pregnancies.

Retinal Artery or Vein Occlusions: Pregnancy is known to be associated with a hypercoagulable state with changes in clotting factors, platelets, and blood flow dynamics. However, increased hypercoagulable states in pregnancy may be linked to non-physiologic systemic changes including: thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulopathy, amniotic fluid embolism, and antiphospholipid antibody syndrome (APLA). Thus, increased coagulability may be linked to the development of certain ocular pathologies including retinal vein and artery occlusions. Both retinal artery and vein

occlusions have been documented in pregnancy. Although retinal vein occlusions are less common than arterial in pregnancy, both have similar symptomatic presentation [31]. Both may present with painless monocular vision loss with varying visual deficits depending on the location of the occlusion. Central artery occlusions have visual loss which is central and dense. Branch artery occlusions involve sections of the peripheral visual field which may go unnoticed [32,33]. Central Retinal vein occlusion may present as a dense central scotoma with subtle intermittent episodes of blurred vision or it may be a sudden, painless monocular vision loss. The nonischemic type is often the more subtle than the ischemic type, with vision loss being more severe and permanent with the ischemia of the choriocapillaris [34].

DIC: There are several obstetric causes of disseminated intravascular coagulation (DIC) during pregnancy and postpartum [11,35]. Disseminated Intravascular Coagulation (DIC) is known to be a complication of pregnancy secondary to common obstetric causes including: amniotic fluid embolism, intrauterine fetal demise (IUFD), preeclampsia/eclampsia, placental abruption, placenta praevia, septic abortion, intrauterine infection, and acute fatty liver of pregnancy [11,35-37].

The choroid is the most common intraocular structure involved during DIC [11,38]. Increased thrombus formation most commonly leads to vascular obstruction within the choroid, specifically the choriocapillaris. Occlusion within the choriocapillaris can cause serous retinal detachment (SRD) through the disruption of the overlying retinal pigment epithelium [35-38].

TTP: Another hypercoagulable state that may occur during pregnancy, resulting in visual changes is thrombotic thrombocytopenic purpura (TTP). TTP causes small vessel thrombosis, thrombocytopenia, microangiopathic hemolytic anemia, altered mental status, renal dysfunction, and fever. Visual changes occur in approximately 10% of patients due to retinal artery narrowing, hemorrhage, serous retinal detachment and optic nerve head edema. The most common visual complaint is a homonymous hemianopia with a scintillating scotoma. Also, subconjunctival hemorrhage and extraocular muscle paresis may be present [39].

APLA: Lastly, antiphospholipid antibody syndrome (APLA) is a hypercoagulable state that may have an increased frequency in pregnancy. APLA clinically presents as recurrent arterial or venous thrombosis which may be associated with recurrent miscarriages. Ophthalmic manifestations may present in the form of vascular thrombosis of the retina, choroid, optic nerve and ocular motor nerves [40].

Ptosis: Ptosis is usually unilateral and can occur in uncomplicated pregnancy. The physiologic stress of labor and delivery, edema, and changes in hormones results in dysfunction of the levator aponeurosis, resulting in ptosis [41,42].

Effect of Pregnancy on Preexisting Ocular Disorders

Pregnancy has an effect on preexisting ocular conditions such as Diabetic retinopathy, Glaucoma, intracerebral tumors, uveitis, multiple sclerosis, and other inflammatory conditions. Thus it is important to understand how these diseases change during

gestation.

Diabetic Retinopathy: With the rise of the obesity epidemic, the number of woman with diabetes during pregnancy has increased over the past decades [43]. Pregnancy itself is a major risk factor for the progression and development of diabetic retinopathy. In particular, the progression of diabetic retinopathy is strongly influenced by a variety of factors including: the duration of diabetes, glycemic control, severity of retinopathy prior to conception, and the presence of hypertension. However, gestational diabetes is not linked with diabetic changes within the eye [44].

The duration of diabetes increases the risk of retinal changes. In other words, the longer the patient has diabetes, the greater the risk for diabetic retinal disease. Thus, it is recommended that women plan their conception during the third decade. Studies have shown that diabetic complications during pregnancy increase dramatically with maternal age [45]. Poor glycemic control also affects the progression of diabetic retinopathy. Higher levels of HbA1C at conception are linked with higher risk of retinopathy. Thus, tight glycemic control should be attained before conception [44-46].

Another important consideration is the severity of retinopathy prior to conception. Regardless of severity, all parturients must have a baseline ophthalmic examination in the first trimester. Women with no existing diabetic retinopathy or mild non-proliferative diabetic retinopathy are at a low risk for retinopathic changes [44]. It is advised that repeat ophthalmic examination occur in the third trimester or earlier if there are visual deficits. Moderate nonproliferative diabetic retinopathy has been associated with progression of retinal changes in the second trimester which may resolve by postpartum or third trimester. Macular edema may also be seen with worsening diabetic retinopathy during the second trimester. It is recommended that ophthalmic examination should increase in frequency to once every trimester. Severe nonproliferative diabetic retinopathy prior to conception may result in increased retinal changes such as blot hemorrhages and cotton wool spots during the second trimester, with possible regression in the postpartum [46]. Ophthalmic examination is recommended every 2 to 3 months because this group has the highest risk of developing proliferative diabetic retinopathy [44]. Proliferative diabetic retinopathy prior to conception needs to be monitored the most extensively. It is recommended that monthly ophthalmic evaluations occur. Some studies show up to 45% of diabetic patients have progression of proliferative diabetic retinopathy during pregnancy. These patients also have higher complications of retinal detachment and vitreous hemorrhage [47]. However, there may be up to a 50% decrease in the rate of progression in women who have laser photocoagulation prior to conception. Interestingly, proliferative retinopathy may regress at the end of the third trimester or postpartum without treatment [45,46].

However, current guidelines from the American Diabetes Association regarding severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy suggest that vigorous aerobic or resistance exercise may be contraindicated. High intensity physical activity may increase the risk of

complications including vitreous hemorrhage or retinal detachment [48].

Table 1: Screening Guidelines for Diabetic Retinopathy.

Screening Guidelines for Diabetic Retinopathy	
All Diabetic Patients	First trimester
No Existing Diabetic Retinopathy	Repeat in the third trimester
Mild Non-Proliferative Diabetic	Repeat in the third trimester
Moderate Non-Proliferative Diabetic Retinopathy	Repeat every trimester
Severe Non-Proliferative Diabetic Retinopathy	Repeat every 2 to 3 months
Proliferative Diabetic Retinopathy	Repeat monthly

Glaucoma: Glaucoma is another preexisting disease modified by pregnancy. As mentioned earlier, intraocular pressure is decreased during pregnancy [11-15]. Intraocular pressure decreases during the second trimester and continues to decrease with the advancing pregnancy [13]. In most cases, lower intraocular pressure means glaucoma improves with pregnancy [49-50]. However, peripheral vision is also affected during pregnancy. During the last trimester of pregnancy, mean threshold sensitivity of the entire central and regional visual field increases [50].

Idiopathic intracranial hypertension: Idiopathic Intracranial Hypertension (IIH) also known as benign intracranial hypertension (BIH) and pseudotumor cerebri is a disease of unknown etiology associated with increased intracranial pressure. It occurs primarily in obese females of child-bearing age usually in their third decade of life [51,52]. BIH also has the greatest propensity to occur in the first trimester [51]. The increased intracranial pressure most commonly presents with headaches. 92% of patients with BIH present with headaches associated with nausea and vomiting which are worse in the morning and exacerbated by Valsalva maneuver [11,51].

Ocular manifestations of Idiopathic Intracranial Hypertension (IIH) include obscuration of vision, diplopia, pulsatile tinnitus, scotomata, photopsias, and retrobulbar pain [11,51]. Papilledema is typically bilateral but may be unilateral or even absent in some cases [51,52]. Most common symptom of papilledema is transient visual obscuration which is described as the dimming of vision of one or both eye for up to 30 seconds. These visual changes often occur due to orthostatic changes in the patient. The patient may also complain of loss of peripheral vision in one or both eyes starting in the nasal inferior quadrant which progresses to the central visual field. The field loss tends to mimic glaucoma field loss. Visual acuity may also be affected [51].

Benign intracranial hypertension does not affect the fetus and has the same prognosis in pregnant versus non-pregnant females. It is recommended that the patient lose weight after the pregnancy. Major goals of idiopathic intracranial hypertension (IIH) treatment include alleviation of symptoms and preservation of visual function [51]. Medical treatment and observation are usually effective [11,51].

Pituitary adenoma: Pregnancy may also affect the growth of pituitary adenomas and microadenomas. Pregnancy stimulates the growth of the prolactin secreting cells within the pituitary, thus increasing the size of the gland [53]. However, most microadenomas or pituitary adenomas are asymptomatic prior to and during pregnancy. However some individuals may become symptomatic once the adenoma progresses to a certain size. The patient may complain of mass-effect symptoms including headache, bitemporal field defects, decrease in visual acuity, and diplopia. Treatment for symptomatic patients includes surgery, radiation, bromocriptine, and corticosteroids depending if the mass is an adenoma or prolactinoma [54]. Treatment is effective and has no interactions on the infant. After pregnancy, pituitary adenomas may regress in size, resulting in no long term visual deficits. It is recommended that parturients with pituitary adenomas and microadenomas have monthly ophthalmic examinations with visual field assessment to rule out enlargement.

Meningioma: Growth of meningiomas may also be affected by gestation, growing rapidly during pregnancy. Parturients become symptomatic once the tumor reaches a certain threshold, complaining of decreased vision and visual field loss [55]. Treatment for symptomatic patients is usual surgical [56]. However, mild symptoms can be observed with treatments occurring in the postpartum.

Inflammatory conditions: Inflammatory disorders such as rheumatoid arthritis, sarcoidosis, and spondyloarthritis have both systemic and ocular manifestations which notably decrease during pregnancy [57]. The decreased symptomatic presentation of these pathologies may be due to rise of corticosteroids found in pregnancy. Symptoms of these inflammatory diseases are usually exacerbated in the postpartum [58].

Toxoplasmosis: Toxoplasmosis may also be affected by pregnancy. There have been known cases of reactivation of ocular toxoplasmosis within the parturient during pregnancy. The fetus's risk for contacting congenital toxoplasmosis is extremely low. Treatment involves spiramycin which has been documented to be safe in pregnancy [59].

Ophthalmic medications: There is much uncertainty regarding the safety of using ophthalmic medications during pregnancy and breastfeeding. Most drug information is derived from animal experimentation due to the lack of clinical trials on pregnant women. Although animal experimentation provides a good foundation for drug safety, findings cannot necessarily be extrapolated to humans. Thus, when any ophthalmic medication is given topically in pregnant or breastfeeding individuals it is recommended that two steps be performed. First, the lowest effective topical dose must be given. Secondly, systemic absorption should be minimized by using nasolacrimal compression and wiping excess medication from the face. Also since topical medication drains into the nasolacrimal ducts with eye blinking, prolonged closure of the eyelids for 1 to 2 minutes will decrease drainage and systemic absorption [60].

Although, one study found pregnant and nursing mothers can undergo most types of ophthalmological examination and treatment without adverse effects to the fetus [22], it is best

to err on the side of caution. The recommendation for the use of ophthalmic medications below is supported by the latest recommendations of the National Registry of Drug-Induced Ocular Side Effects and FDA [61].(Table 2-4)

Table 2: Glaucoma Medication in Pregnancy [64].

Glaucoma Medication in Pregnancy [64]	
Beta-blocker (Timolol, Levobunolol, Betaxolol, Carteolol)	<ul style="list-style-type: none"> • Avoid during first trimester • Avoid in breastfeeding becomes concentrated in breast milk • Discontinued 2-3 days prior to delivery
Carbonic Anhydrase Inhibitors (Acetazolamide, Dorzolamide, Brinzolamide)	<ul style="list-style-type: none"> • Acetazolamide contraindicated in pregnancy and breastfeeding • Acetazolamide is a potential teratogen impairs renal and hepatic function • Dorzolamide and Brinzolamide not contraindicated but risks unknown
Miotics (Pilocarpine, Echothiophate, Carbachol)	<ul style="list-style-type: none"> • Appear safe during pregnancy but risk during pregnancy and breastfeeding cannot be ruled out • Pilocarpine’s risk cannot be ruled out, use not recommended
Alpha-Adrenergic Agonist (Brimonidine)	<ul style="list-style-type: none"> • No fetal risk in animal studies but none done on humans • Unknown if excreted in breast milk
Prostaglandin Analogs (Latanoprost, Travoprost, Bimatoprost)	<ul style="list-style-type: none"> • Most data for Latanoprost • Conflicting reports • Caution use during pregnancy and breastfeeding

Table 3: Diagnostic Ophthalmic Medication in Pregnancy [64].

Diagnostic Ophthalmic Medication in Pregnancy [64]	
Topical Anesthetic (Tetracaine, Lidocaine, Proparacaine)	<ul style="list-style-type: none"> • No known teratogenic effect during pregnancy • No known effect on breastfeeding
Fluorescein	<ul style="list-style-type: none"> • No known teratogenic effects • Excreted in breast milk • Caution in breast feeding individuals
Mydriatics (Atropine, Epinephrine, Phenylephrine, Tropicamide)	<ul style="list-style-type: none"> • Safe for single use • Repeated use is contraindicated due to teratogenic effects • All contraindicated during breastfeeding

Table 4: Additional Ophthalmic Medication in Pregnancy [64].

Additional Ophthalmic Medication in Pregnancy [64]	
Antibiotics (Erythromycin, Ophthalmic Tobramycin, Ophthalmic Gentamicin, Polymyxin B, Quinolones)	<ul style="list-style-type: none"> • Safe in pregnancy • Polymyxin B is safe during lactation
Antibiotics (Chloramphenicol, Systemic Gentamicin, Neomycin, Rifampin, Tetracycline, Systemic Tobramycin)	<ul style="list-style-type: none"> • Avoid during pregnancy
Corticosteroids (Prednisolone)	<ul style="list-style-type: none"> • Topical safe during pregnancy but unknown during breastfeeding • All systemic corticosteroids are contraindicated
NSAID (Diclofenac)	<ul style="list-style-type: none"> • No evidence of risk • Little concern for safety during pregnancy
Antivirals (Acyclovir, Valacyclovir, Famciclovir, Ganciclovir)	<ul style="list-style-type: none"> • Safe during pregnancy • Acyclovir, Valacyclovir appear to be safe during breastfeeding

Conclusion

Pregnancy provides a great opportunity for physicians to establish care in a younger population who otherwise would not seek medical attention. As a result, physicians are able to treat and screen for several common pathologies during pregnancy. Certain ocular changes, whether physiological or pathological, may be increased during pregnancy. Thus, it is important to be educated on pathophysiological changes that are common in pregnancy in order to better counsel women who are pregnant or planning to become pregnant [62]. Although many ocular changes are mild, temporary, and require little to no treatment, all ocular symptoms in pregnancy requires ophthalmologic examination and management [63]. However, long term data on ophthalmic drugs during pregnancy and lactation is insufficient [60,64]. Thus, doctors should always be cautious and consult expert opinion before using any topical or systemic treatment on the patient [60].

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