Review Article

Motherhood: What every ophthalmologist needs to know

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The aim of this review article is to summarize the available literature on physiologic and pathologic ocular changes during pregnancy and the effect of diseases in pregnancy. A literature search was conducted using PUBMED, MEDLINE, and Cochrane library in English. In addition, the cited references in the published articles were manually reviewed for the relevant results. Pregnancy encompasses a multitude of changes in all body systems, including the visual system of the female. The changes can be physiological, i.e., changes occurring in the lids and adnexa, cornea, conjunctiva, changes in tear film composition and intraocular pressure, retina, choroid, and visual field. Pathological changes in a pregnant woman's eye include changes related to preeclampsia and eclampsia, central serous chorioretinopathy, retinal artery or vein occlusions, and disseminated intravascular coagulation. Preexisting diseases like diabetic retinopathy, Graves' disease, idiopathic intracranial hypertension, various inflammatory conditions can undergo changes in their course during pregnancy. Ophthalmic medications can have an effect on both mother and the baby and hence should be used cautiously. In addition, intrauterine infections play a major role in causing inflammation in the eye of the baby. Hence, vaccination of the mother prior to pregnancy plays an important role in preventing intrauterine infections in the neonate. A regular eye examination in the perinatal period plays a vital role in recognizing ophthalmic pathologies which might require a prompt medical intervention. Pathological ocular diseases should be discriminated from physiologic changes to establish an individualized treatment or preventive plan. This approach to ocular benefits of treatment to the mother should always weigh against the potential harm to the fetus.

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Pregnancy affects almost each and every system of the body. Apart from hematological, cardiovascular, and immunological changes, ocular changes in pregnancy are fairly common. While most of these changes are transient in nature and require no treatment, some changes may remain permanent. As in the case of other body systems, changes in eye during pregnancy can be broadly divided into Physiological changes, which are the changes that occur normally during pregnancy; Pathological changes, which present for the first time in pregnancy or existing diseases affected by pregnancy.[1] Knowledge of physiological changes is important to avoid overtreating the patient, whereas treatment of chronic diseases is a delicate balance between preventing the disease progression in the mother and avoiding interventions that might be potentially harmful to the fetus.

The aim of this review article is to summarize available data in the literature on the pregnancy-induced ocular changes to discriminate between benign and pathological conditions and gives an insight for the management of the pathologies.

Methods

We searched the PubMed database and Cochrane review for publications up to October 2019 with the keywords "eye," "diabetic retinopathy," "pre-eclampsia," "pregnancy," "drugs in pregnancy," and "congenital infections" and supplemented the findings with articles from the reference lists of earlier reviews. We went through the relevant articles which were reviewed and also relevant studies and book chapters reporting data on any ocular changes in pregnant women were included in this review.

Physiological Changes

Both structural and functional changes can occur in the eye during pregnancy.

Lids and adnexa

The most frequently encountered problem among pregnant women is an increase in pigmentation around the cheeks and eyes, i.e., chloasma, and is commonly seen during pregnancy.[2] Also known as pregnancy mask, it is caused by an increase in the progesterone, estrogen, and melanocyte-stimulating hormone levels during pregnancy.[3] Fluid retention and hormonal changes during pregnancy cause defect in levator aponeurosis resulting in unilateral or bilateral ptosis.[4] Usually all the changes resolve in post-partum period. Exophthalmos is not a common finding and presence of it should warrant aggravation or diagnosis of preexisting Graves' disease.[5]

Tear film composition

Hormonal changes are among the most prominent changes during pregnancy.[6] Total testosterone levels are found to

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increase from the first to third trimester. There is a concurrent increase in steroid hormone-binding globulin with a reduction in circulating active and free testosterone.[7,8] The secretion of estrogen and progesterone is also found to increase during pregnancy, being more prominent in the third trimester and can lead to dry eye.[8] The mechanisms which can lead to Dry eye disease (DED) include:

a. The interplay between the levels of estrogen and testosterone. Testosterone enhances the development and differentiation of the meibomian gland and estrogen; on the other hand, it promotes acinar cell death, leading to a reduction in the size and secretions from the gland.[9,10]
b. Pregnancy enhanced immune-reactivity of prolactin, transforming growth factor beta 1, and epidermal growth factor in the ductal cells can cause direct damage to lacrimal acinar cells.[11]
c. Increased viscosity is attributed to the lysozyme component in the tear film which causes dry eye.[12]
d. Dry eye disease in pregnancy is also partly attributed to the dehydration state in first trimester due to excessive nausea and vomiting and the medications used to treat them.[11] Contact lens usage should be avoided during pregnancy as it leads to increased dryness.[11]

Cornea, conjunctiva, and intraocular pressure (IOP)

Fluctuations in hormonal levels and presence of sex hormone receptors in cornea during third trimester and early post-partum period cause an increase in corneal curvature and thickness due to corneal edema. This results in intolerance to contact lenses.[1,13] and hence should be avoided during pregnancy. Corneal sensitivity starts decreasing at approximately 31 weeks of gestation.[14]

Initial studies stressed upon fluctuating levels of estrogen, progesterone, relaxin, and Beta HCG as a cause of decreased intraocular pressure. Later it was reported that an increase in aqueous outflow rather than a decrease in aqueous formation resulted in a decreased IOP during pregnancy.[15,16] Ocular hypertensives may show improvement in IOP during pregnancy for the same reason and pregnancy may even bring the IOP down to within normal limits.[17]

It was also found that the mean intraocular pressures were higher in the first trimester and in the puerperal period than in the third trimester. Some authors have also reported an increased central corneal thickness during these trimesters than during the first trimester and the first 3 months after childbirth.[18,19]

Refractive error and accommodation

Transient loss of accommodation owing to change in the curvature of crystalline lens is commonly seen during lactation and pregnancy.[20] There is fluid retention which affects the refractive power due to myopic shift and so the glasses prescribed may become irrelevant after the pregnancy. The current recommended protocol is to postpone the changes in the glass prescription until few weeks postpartum. In addition, due to unpredictability in the refractive power, refractive surgery should be deferred till a stable postpartum refraction.[21]

Retina, choroid, and visual fields

The physiological pituitary enlargement can result in changes in visual field ranging from bitemporal hemianopia, concentric reduction in the visual field, and homonymous hemianopia.[12] The choroid is a highly vascularized tissue which is susceptible to the ongoing hemodynamic and hormonal changes in pregnancy.[22] Choroidal thickness has been reported to increase in pregnancy, with the maximum increase occurring in the second trimester.[23-26] Blood pressure decreases during pregnancy and then increases sometimes to supra-normal levels in third trimester. Blood volume increases during pregnancy, with the peak occurring in the second trimester. In addition, pregnancy is a known hypercoagulable state, increasing the chances of clot formation. All these changes are reflected in the retinal vasculature as well.

Pathological changes

There are few pathological eye changes specifically related to the pregnant state of the female.

Preeclampsia and eclampsia

Preeclampsia, the most frequently encountered medical complication of pregnancy, is characterized by elevated systemic blood pressure (>140/100 mmHg), proteinuria (>300 mg/24 h), and generalized edema, and it typically appears after the 20th week of pregnancy, while eclampsia is characterized by preeclampsia with seizures.[27] Preeclampsia and eclampsia patients are at risk of developing retinal and choroidal dysfunction which may even lead to vision loss. Focal narrowing of the retinal arterioles which may be generalized as well is the most common finding in preeclampsia-related retinopathy. These patients can have hypertensive retinopathy findings such as hemorrhages, papilledema, and subretinal fluid accumulation.[28] Other complications which may be associated with preeclampsia include retinal or vitreous hemorrhages, cortical blindness, serous retinal detachment, and central retinal vein occlusion (RVO). Patient usually complains of blurring of vision, flashes of lights, and visual field complaints. Cortical blindness can occur in late pregnancy or shortly after delivery in severe preeclampsia or eclampsia due to involvement of occipital lobes.[29,30] The degree of retinopathy correlates with the severity of preeclampsia and hence is important for both ophthalmologist and gynecologist.

Central serous chorioretinopathy

The previous studies have described central serous chorioretinopathy as a possible ocular complication of pregnancy with an annual incidence of 0.008%.[31] It usually resolves spontaneously after delivery, with minimal or no sequel. Kitzmann *et al*. reported on the incidence of CSR in pregnant females (9%) in a population-based study.[32] Quillen *et al*. in their study reported a small percentage (5%) of pregnant patients with CSC who developed a more severe form with extensive retinal detachments and severe visual loss.[33] It occurs due to an increase in catecholamine levels during pregnancy causes an increase in cortisol levels in the third trimester. In addition, vasomotor stress in pregnancy may lead to choroidal dysfunction which might play primary pathophysiologic role in this disorder.

This is characterized by a serous detachment of the sensory retina. It commonly appears in third trimester and resolves spontaneously in the postoperative period. Patient usually complains of metamorphopsia, decreased vision, central scotomas, and loss of color and contrast sensitivity. Possible mechanisms include changes in vascular permeability and autonomic functions during pregnancy. Studies have reported that subretinal fibrin deposits are seen in almost 90% of pregnant patients.[34]

Retinal artery or vein occlusions

Park *et al*. in their study suggested that normal pregnancy is a protective factor and not a risk factor for the development

of RVO.[35] Preeclampsia and eclampsia are associated with a significantly higher incidence of RVO in pregnancy.[36,37] This occurs due to poor placental perfusion resulting in endothelial dysfunction and retinal vascular abnormalities. The incidence of RVO in pregnancy is significantly lower than general female population of the same age, with only 33 cases of approximately 1.8 million deliveries.

Pregnancy is a hypercoagulable state with an increase in fibrinogen and other clotting factors.

Purtscher's-like retinopathy has been reported in immediate post-partum period with fundus findings revealing widespread cotton wool spots with or without intraretinal hemorrhages.

Complement activation and leucocyte aggregation lead to the formation of emboli in the retinal arterioles and manifest as Purtscher's retinopathy.

Hypercoagulable states in pregnancy can lead to thrombotic thrombocytopenic purpura (TTP), disseminated intravascular coagulopathy, amniotic fluid embolism, and antiphospholipid antibody syndrome (APLA).[38] They are associated with retinal arterial or vein occlusions [Fig. 1], with vein occlusions being more common than arterial occlusion.[39]

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) occurs due to the systemic activation of intravascular coagulation. It occurs due to severe preeclampsia, intrauterine fetal death, and amniotic fluid embolism. Choroid is most often involved in DIC. Occlusion of choriocapillaris causes separation of pigment epithelium causing serous retinal detachment. Patient complains of decreased vision. The detachment is thought to be a consequence of dysfunction of retinal pigmentary epithelial pump mechanisms.[40] Vision usually returns to normal in the postoperative period with residual pigmentary changes.

Effect of Pregnancy on Preexisting Ocular Diseases

Diabetic retinopathy

Pregnancy is a risk factor in the progression and severity of diabetic retinopathy. Risk factors for the progression of diabetic retinopathy include duration of diabetes, glycemic control, and presence of hypertension. The duration of diabetes is one of the most important factors implicated in the progression of diabetic retinopathy. The longer the duration of diabetes, the higher the chances to develop diabetic retinopathy.[41-43] Also a poor glycemic control in terms of higher HbA1c at the time of conception is linked with a higher tendency to develop retinopathy. Blood glucose is also an important determinant in fetal well-being. Well-controlled blood glucose levels prior to conception may reduce the risk of spontaneous abortion and fetal morbidity and mortality.

All women in the reproductive age group should be counseled about the importance of strict glycemic control prior to conception. Any diabetic woman prior to pregnancy should undergo a complete ophthalmological evaluation with regards to fundus examination. Patients with no retinopathy to moderate nonproliferative diabetic retinopathy should be reexamined every 3 to 12 months [Fig. 2]. Patients with severe nonproliferative diabetic retinopathy [Fig. 3] and proliferative diabetic retinopathy should be reevaluated every 1 to 3 months.

Graves' disease

Graves' disease is one of the most important causes of hyperthyroidism in pregnancy. Graves' disease aggravates in the first trimester and after delivery, but improves in the second and third trimester.[28] Rarely, the fetus can be affected because of trans placental passage of maternal IgG. Pregnant female with Graves' orbitopathy is treated in the same manner as in a nonpregnant female. Mothers with active Graves' disease should be treated with antithyroid drugs, because in untreated cases, there is high fetal morbidity and mortality.

Glaucoma

The pregnant glaucoma patient often poses a challenge for the clinician as the risk of glaucoma progression in the mother has to be balanced against the possible teratogenic effects in the fetus. As mentioned earlier, intraocular pressure decreases during pregnancy. In most cases, lower intraocular pressure means glaucoma improves with pregnancy.[19,44] The decrease in intraocular pressure has the potential advantage of avoiding the side effects of antiglaucoma medications. Medical management of glaucoma carries a risk to the normal development of the fetus. It is advisable to instill these drugs along with punctal occlusion to avoid side effects due to systemic absorption.[44,45]

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.[44]

Idiopathic intracranial hypertension or Benign intracranial hypertension (BIH) or Pseudotumor cerebri

It is a disease of unknown etiology associated with increased intracranial pressure. It is mostly seen in obese females of childbearing age in their third decade of life.[46,47] BIH also has the highest propensity to occur in the first trimester.[41] Patients with BIH most commonly present with headaches.

Ophthalmic manifestations of idiopathic intracranial hypertension (IIH) include obscuration of vision, diplopia, scotoma, photopsia, and retrobulbar pain.[5,46] Papilledema is usually bilateral but may be unilateral or even absent in some cases.[46,47] Papilledema most commonly presents as transient obscuration of vision which is described as the dimming of vision of one or both eyes for up to 30 s, which often occurs due to orthostatic changes in the patient. Some patients may also complain of loss of vision in the nasal inferior quadrant which progresses to the central visual field. This can lead to complete loss of vision.[46]

Major goals of IIH treatment include alleviation of symptoms and preservation of visual function.[46] Medical treatment and observation are usually effective.[5,46]

Inflammatory conditions

Inflammatory disorders such as sarcoidosis, and other spondyloarthropathies which have both systemic and ocular manifestations decrease during pregnancy due to the rise of endogenous corticosteroids.[48] This is beneficial for women with chronic sight-threatening symptoms due to uveitis, as it lessens the need for immunosuppressants which might have potential teratogenic effects on the fetus.[49]

Toxoplasmosis

Maternal TORCH infections need to be monitored closely as they are a major cause of inflammation in the neonatal eye [Fig. 4]. Few cases of reactivation of ocular toxoplasmosis have

been notedduringpregnancy [Fig. 5]. Spiramycinastreatmentis found to be safe in pregnancy.[50]

Neuroophthalmological Changes in Pregnancy

Various neuroophthalmic changes which have been listed during pregnancy include:

- Venous sinus thrombosis
- Pituitary adenoma and meningioma
- Pseudotumor cerebri (Benign intracranial hypertension)
- Optic neuritis and neuropathy
- Other neuroophthalmologic disorders.

Disorders Related to Labor and Delivery

Purtscher's-like retinopathy has been reported in few studies within 24 h of childbirth. Although Purtscher's retinopathy can be rarely seen in pregnancy, it has always been associated with complicated deliveries.[51,52] No case has been documented following normal spontaneous delivery.

Jeon *et al*. in their study reported the first case of Purtscher's-like retinopathy developed after preeclampsia combined with acute pancreatitis in Korea.[53] Purtscher's-like retinopathy is rare in women with preeclampsia, but some cases with permanent visual loss have been reported.[54,55] Hence, in any pregnant females presenting with visual disturbances, this condition should be ruled out.

The patient may complain of unilateral or bilateral loss of vision, with widespread cotton wool spots with or without intraretinal hemorrhages seen on fundus. Bilateral retinal arteriolar occlusions from amniotic fluid particles have been reported.[56]

Valsalva maculopathy can be caused by rapid rise of intravenous pressure during delivery which may cause a sudden decrease in vision resulting from preretinal, subretinal, or vitreous hemorrhage. If there is retinal detachment, cesarean section or forceps delivery is preferred.[57]

Considering childbirth as a forthcoming traumatic event, pre and posttraumatic stress disorder in some females can lead to accidental injuries in the eye, including corneal and conjunctival abrasions. Owing to this stress, few women can also develop

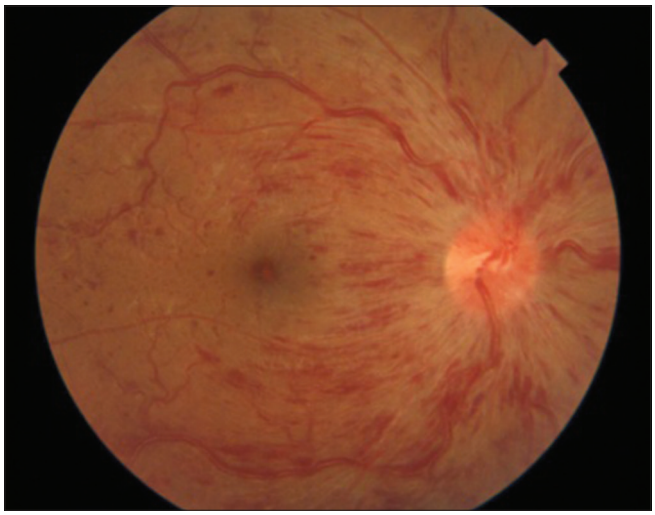

Figure 1: Fundus photo showing central retinal vein occlusion in right eye

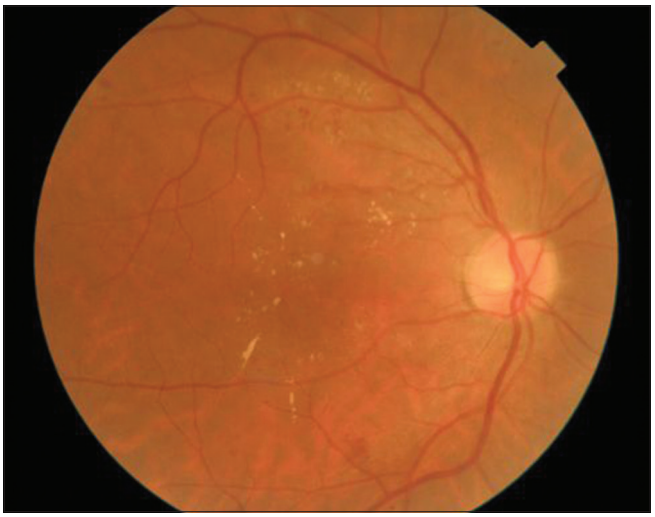

Figure 2: Fundus photo showing mild nonproliferative diabetic retinopathy in right eye

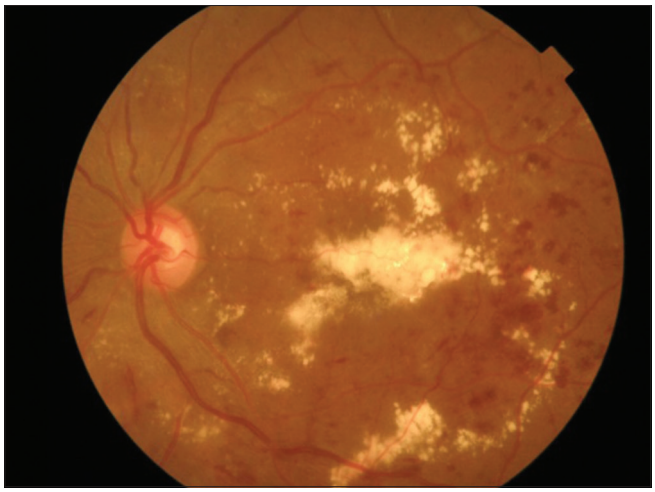

Figure 3: Fundus photo showing severe nonproliferative diabetic retinopathy in left eye

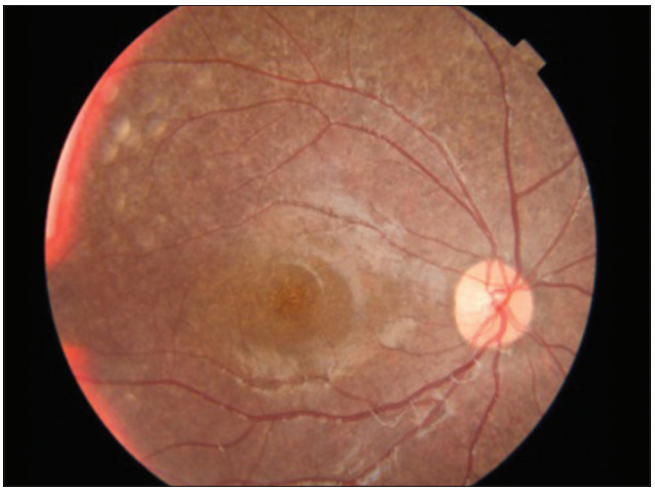

Figure 4: Fundus photo showing salt and pepper retinopathy in right eye in a child

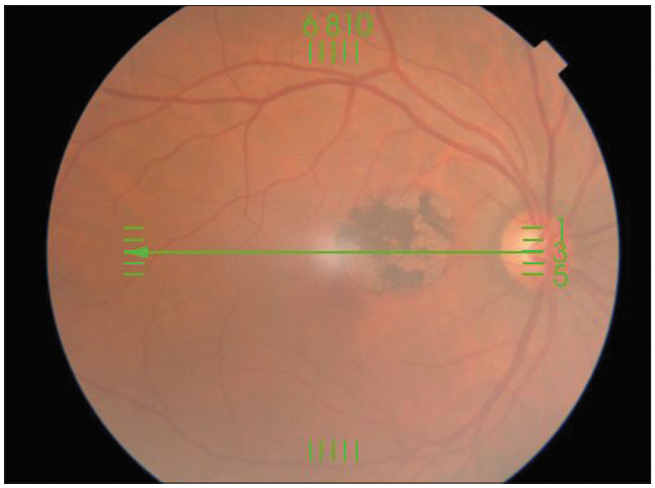

Figure 5: Fundus photo showing macular scar in toxoplasmosis

trichotillomania, which is an irresistible urge to pull out their hair from the scalp, eyelashes, and eyebrows.

Ocular changes during labor

Sheehan's syndrome

Sheehan's syndrome or Pituitary apoplexy occurs as a result of ischemic pituitary necrosis due to severe postpartum hemorrhage. Symptoms associated may be sudden onset of headache, visual loss, ophthalmoplegia, enlargement of pituitary gland, small sella size, and DIC.[28,58]

Effect of Ophthalmic Medications on Pregnancy

The lowest possible dosage should be used while using the topical medications, as they may lead to harmful effects on the mother and the fetus.

FDA have listed 5 categories-A, B, C, D or X to indicate the potential of a drug to cause birth defects if the drug was used during pregnancy.[59]

Class A-Well-controlled studies in pregnant women have not shown any risk to fetus.

Class B-No evidence of risk in humans.

Class C-Human studies are lacking, and animal studies are either positive for fetal risk or inadequate as well.

Class D-Investigational or postmarketing data shows some risk to fetus, so there is definite evidence of risk.

Class X-Studies in animals or human or investigational or postmarketing reports have shown fetal risk and thus is contraindicated in pregnancy.

Precautions which can be taken to minimize systemic absorption include nasolacrimal compression and temporary punctal occlusion.[60]

Antiglaucoma medications

Beta blockers

Topical beta-blockers come under FDA risk category C in the first trimester and can cause intrauterine growth retardation if used in 2nd and 3rd trimester (FDA risk category D) and persistent neonatal blockade if used near term. They should be avoided during pregnancy and should be discontinued 2 to 3 days before delivery to avoid inhibiting uterine contractility. They also raise concerns regarding neurological, pulmonary, and growth restriction complications in the newborn.[61-63] Neurological problems stem from the side effects of lethargy, confusion, and depression due to beta-blocker usage. Studies have shown the advantage of betaxolol over timolol in preventing these neurological side effects.[64,65] Cardiovascular side effects stated in some studies include bradycardia and arrhythmias.[66] These drugs are actively secreted in breastmilk and hence they are perhaps avoided during lactation.[60,67,68]

Carbonic anhydrase inhibitors

Carbonic anhydrase inhibitors are listed under category C drugs for use during pregnancy. Topical and systemic carbonic anhydrase inhibitors are potentially contraindicated during pregnancy due to their potential teratogenic effects. They are also perhaps avoided during lactation because of adverse renal and hepatic effects in the infant.[60,67,68]

Prostaglandin analogues

Come under FDA risk category C. Systemically given prostaglandins have been shown to induce labor. However, it has not been ascertained whether topically given prostaglandins reach a plasma concentration which can affect the development of the fetus.[69] Their role during pregnancy and lactation is controversial, hence is generally avoided during this period.[60,67] Punctal occlusion should be explained to the patients using category C drugs to reduce systemic absorption of the drugs and avoid systemic side effects.

Mydriatics

Can be used occasionally for the retinal examination. Repeated use of mydriatics is perhaps avoided owing to the potential teratogenic effects of both parasympatholytics and sympathomimetics.[12,60,67]

Infants for screening with retinopathy of prematurity may be dilated with cyclopentolate 0.2% and phenylephrine 1% or in cases with more heavily pigmented infants, cyclopentolate 0.5% or tropicamide 1%, or both, and phenylephrine 2.5% may be substituted and instilled twice.[70]

Corticosteroids

Topical corticosteroids come under FDA risk category B. Systemic corticosteroids are contraindicated in pregnancy since they cause teratogenic effects, stillbirths, and intrauterine growth retardation.[71] There are evidences of no teratogenic effects and adverse pregnancy outcomes of topical steroids in pregnancy and lactation, but they should be avoided whenever possible.[12,60,67,71]

Antibiotic eye preparations

Safe antibiotics during pregnancy include erythromycin and polymyxin b, while polymyxin b and the sulfonamides are also safe during lactation. Aminoglycosides and fluoroquinolones should be avoided during pregnancy.[60,67]

Antiviral eye preparations

Come under FDA risk category B. Role of teratogenic effects of topical acyclovir has not been studied in pregnant woman; hence, it should be used cautiously in pregnancy and lactation.[12,60,67]

Fluorescein dye

Comes under FDA risk category B. No known teratogenic effects are known, but most of the retinal specialists avoid

fluorescein angiography during pregnancy, especially during first trimester.[12,67]

Topical anesthesia

Topical anesthetic drops can be used safely during pregnancy.

Antiallergic eye drops

Mast cell stabilisers (FDA risk category B) are safe in pregnancy, while antihistaminic eye drops (FDA category C) should be avoided.[12,60,67]

Anti-Vascular endothelial growth factor (VEGF)

Few studies have demonstrated the role of VEGF in the maintenance of fetal and placental vasculature and reduced VEGF expression was linked with defective embryogenesis and fetal loss in humans.[71-73] Therefore, use of anti-VEGF potentially may cause spontaneous miscarriage when administered to pregnant women, though it is more common in women with risk factors such as age more than 35 years, hypertension, diabetes, or previous miscarriages.[74]

Pegaptanib is classified as Category B drug while ranibizumab, bevacizumab, and aflibercept are classified as FDA Category C. The use of anti-VEGF drugs during pregnancy is controversial because they may potentially cause systemic side effects in the mother and fetal harm, as spontaneous miscarriage and preeclampsia.

However, certain diseases for instance diabetic retinopathy, cystoid macular edema in case of uveitis warrant the use of anti-VEGF. Therefore, some authors advocate the use of anti-VEGF after weighing the risk-benefit ratio in individual case.[75]

Conclusion

It is very important for ophthalmologists to be aware of various physiological and pathological conditions that may arise or be altered during pregnancy, and to have knowledge about the differential diagnosis, treatment, and monitoring. It is important to strategically respond to patients with these complaints to prevent possible risks to mother and baby. In addition, since ophthalmic medications can have an effect on both the mother and the baby, they need to be prescribed with extra caution. Drugs like erythromycin, polymyxin b, acyclovir, and amphotericin B can be prescribed safely in pregnancy.

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Conflicts of interest

There are no conflicts of interest.

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