Ocular disease in pregnancy

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Purpose of review

Pregnancy may cause ocular changes, both physiologic and pathologic, and may be associated with the development of new disease or may alter the course of preexisting disease. This paper discusses these changes and reviews diabetic retinopathy, uveitis, preeclampsia, cortical blindness and central serous chorioretinopathy.

Recent findings

Recent reports have contributed to our understanding of the pathophysiology of diabetic retinopathy and cortical blindness associated with preeclampsia, the impact of pregnancy on the course of inflammatory eye disease, and the use of optical coherence tomography in following central serous chorioretinopathy in pregnant women.

Summary

This improved understanding of the pathophysiology of ocular disease in pregnancy and the impact of pregnancy on the course of preexisting ocular disease offers the opportunity for meaningful counseling of women who are pregnant or planning to become pregnant.

Keywords

cortical blindness, diabetic retinopathy, eclampsia, eye disease, preeclampsia, pregnancy, pregnancy-induced hypertension, uveitis

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Abbreviations

ADC	apparent diffusion coefficient
CSCR	central serous chorioretinopathy
DWI	diffusion-weighted imaging
ERD	exudative retinal detachment
MRI	magnetic resonance imaging
NPDR	nonproliferative diabetic retinopathy
VKH	Vogt-Koyanagi-Harada disease

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Introduction

Pregnancy is associated with changes involving multiple organ systems, including the eyes. Ocular physiologic changes are well documented, including a decrease in corneal sensitivity [1] and increases in corneal thickness [2] and curvature [3]. These changes may produce temporary refractive changes and contact lens intolerance [3]. Decreased intraocular pressure is measured during pregnancy, particularly in the third trimester. Noncontact tonometers were recently shown to increase intraobserver agreement in intraocular pressures measured late in pregnancy and may be superior to both Goldmann and Schiötz tonometers in the management of pregnant patients [4].

Pregnancy may alter the course of a preexisting ocular condition, as in diabetic chorioretinopathy and uveitis; may cause a condition specific to pregnancy, such as cortical blindness associated with pregnancy-induced hypertension; or may contribute to the development of conditions also seen in nonpregnant patients, such as central serous retinopathy. We discuss these disorders and offer recommendations for preconception and pregnancy counseling of female patients.

Pregnancy and preexisting ocular disease

Preexisting ocular diseases that can be exacerbated in pregnancy include diabetic retinopathy and uveitis.

Diabetic retinopathy

Pregnancy is considered an independent risk factor for progression of diabetic retinopathy, a leading cause of preventable blindness [5]. Other risk factors for acceleration of diabetic retinopathy in this population include duration of diabetes [6], pregnancy-associated hypertension and preeclampsia [7], rapid normalization of glucose levels during pregnancy [6], poor prepregnancy glycemic control [6], and changes in retinal blood flow [8]. Interestingly, gestational diabetes in the absence of preexisting diabetes does not show a similar association with diabetic retinopathy [9].

In recent studies of insulin-dependent diabetic women, progression of diabetic retinopathy during pregnancy and the postpartum period was correlated to levels of various proinflammatory markers, vasoactive mediators, and angiopoietic factors. Levels of C-reactive protein were found to be higher in women with disease progression and worse glycemic control [10••]. Measures of the vasoactive mediators renin and aldosterone were significantly lower in diabetic pregnancies, as well as during the postpartum period, when compared with their nondiabetic counterparts. The

lower levels did not necessarily correlate with progression of retinopathy [11•], however. Levels of circulating angiopoietic factors were also found not to be associated with progression of pregnancy-related retinopathy [12•].

Severity of diabetic retinopathy at baseline is another strong predictor of disease progression. According to the Diabetes in Early Pregnancy Study [6], 10.3% of women with no retinopathy and 21.1% of women with microaneurysms but no other retinopathy had disease progression during or after pregnancy. Mild nonproliferative diabetic retinopathy (NPDR) progressed in 18.8% of diabetic women (6.3% to proliferative diabetic retinopathy [PDR]), whereas moderate NPDR progressed in 54.8% of cases (29% to PDR). Complications of PDR that may require surgery, including combined rhegmatogenous and tractional retinal detachment and neovascular glaucoma, are associated with a worse visual outcome [13•].

Treatment of pregnant women with diabetic retinopathy depends on the severity of the disease at conception (Table 1). Women without evidence of retinopathy or with microaneurysms only should be evaluated during their first trimester and again with any visual complaints, such as floaters, blurry vision, or loss of vision. Evaluation of patients with mild or moderate NPDR should include an initial dilated examination and fundus photography during the first trimester. Those with mild retinopathy should be reevaluated during the second trimester and monthly during the third trimester. Patients with retinopathy more severe than mild NPDR should have retinal examinations every 4–6 weeks. Most progression will occur by the end of the second trimester [14]. Current recommendations for treatment include laser photocoagulation in pregnant patients who show severe pre-PDR. Waiting until the early proliferative stage may lead to complications that require extensive vitreoretinal surgery [13•], which is more difficult in pregnancy. PDR requires laser photocoagulation to slow further progression and surgical treatment of any complications. The most important intervention is early education. Ideally, patients will have good glucose control and diabetic retinopathy will be treated prior to conception. This should be discussed with all diabetic women of childbearing age.

Regression of diabetic retinopathy is believed to be common during the postpartum period [15]. Despite this, women are at an increased risk of progression for as long as 1 year postpartum and may experience complications such as vitreous hemorrhage and retinal detachment if the condition is not recognized and treated [16••]. Careful monitoring of patients should continue in the postnatal period for 1 year in an attempt to prevent these rare, but devastating, complications.

Uveitis

The impact of pregnancy on the course of inflammatory eye disease is not well established. The literature on the topic is comprised largely of case reports and case series, many addressing Behçet's disease, probably because of its systemic nature, with little attention to other causes of noninfectious uveitis. In addition, although the literature addresses the occurrence of disease exacerbations, no large study has examined visual outcomes in uveitis patients who have been pregnant.

Rabiah and Vitale [17] examined the course of noninfectious uveitis during pregnancy and the postpartum period in 76 pregnancies in 50 women, including patients with Behçet's disease, Vogt-Koyanagi-Harada disease (VKH), and idiopathic uveitis (including acute and chronic anterior, intermediate, and panuveitis). Uveitis exacerbations occurred during the first 4 months of pregnancy in 64% of cases, later in pregnancy in 22%, and within 6 months postpartum in 64%. Fifty-eight percent of pregnancies had one exacerbation, 14% had two, and 28% had none. Exacerbations of uveitis occurred during 85% of pregnancies in patients with VKH, 47% in patients with Behçet's

Table 1. Recommendations for monitoring of pregnant patients with diabetic retinopathy

Retinopathy prior to pregnancy[a]	First trimester	Second trimester	Third trimester
No DR	Dilated eye exam	As needed for visual complaints	As needed for visual complaints
Microaneurysms only	Dilated eye exam	As needed for visual complaints	As needed for visual complaints
Mild to moderate NPDR	Dilated eye exam Fundus photography	Dilated eye exam once for mild and every 4–6 weeks for moderate and severe NPDR (more frequently as needed)	Dilated eye exam every 4–6 weeks or more frequently as needed
Preproliferative DR	Dilated eye exam Fundus photography Laser photocoagulation, if severe	Dilated eye exam every 4–6 weeks or more frequently as needed Laser photocoagulation, if severe	Dilated eye exam every 4–6 weeks or more frequently as needed Laser photocoagulation, if severe
Proliferative DR	Dilated eye exam Fundus photography Laser photocoagulation	Dilated eye exam Fundus photography Laser photocoagulation	Dilated eye exam Fundus photography Laser photocoagulation

[a]Often based on examinations performed early during the first trimester.

disease, and 75% in patients with idiopathic uveitis. Preconception disease activity and treatment did not predict subsequent disease activity.

A study comparing women with Behçet's disease, those with recurrent oral ulcers who did not have Behçet's disease, and controls showed that only two of 10 patients with Behçet's disease had an exacerbation during pregnancy or the puerperium; neither were of uveitis [18]. One woman with recurrent ulcers developed anterior uveitis during pregnancy and thus Behçet's disease was diagnosed. The risk of pregnancy complications and prenatal death was not higher in patients with Behçet's disease. Higher rates of disease exacerbation were reported in another study, with 18 of 25 patients (66.7%) having a flare of Behçet's disease during pregnancy [19]. One of these flares was of skin disease and uveitis. Rabiah and Vitale found that about half of pregnancies (19 pregnancies in 10 patients) were associated with a uveitis exacerbation during pregnancy. More striking, though, is that 84% of pregnancies in Behçet's disease patients in this series were complicated by a uveitis recurrence within 6 months of delivery. Different patient populations were included in these studies, perhaps accounting for the disparate frequencies of exacerbations reported in the different series. For example, the Rabiah and Vitale series specifically studied only Behçet's disease patients with uveitis.

Various other types of uveitis are mentioned in the literature. Progression of subretinal fibrosis 3 months postpartum in a patient with idiopathic multifocal choroiditis has been described [20]. In one study of juvenile idiopathic arthritis, none of the patients with chronic iridocyclitis had an exacerbation during pregnancy, whereas 7% (three of 42) of these patients experienced a uveitis flare within 1 year of delivery [21]. The series by Rabiah and Vitale showed that 85% of pregnancies in patients with VKH (33 pregnancies in 23 patients) were associated with a uveitis flare during pregnancy, with the majority occurring during the first 4 months. About half of pregnancies were associated with a flare within 6 months postpartum. In the same series, 67% of pregnancies in patients with idiopathic uveitis were associated with flares during early pregnancy, with 25% of cases flaring within 6 months of delivery.

A recent study of disease activity and levels of female hormones and cytokines during pregnancy and the postpartum period in four women with chronic uveitis revealed that disease activity was slightly worse in the first trimester and within 3 months postpartum [22•]. The only cytokine consistently detected was transforming growth factor-β, a T-helper 3 cytokine, and its serum levels remained relatively constant during pregnancy and postpartum. As expected, there was marked elevation of levels of estrogen, progesterone, and prolactin during pregnancy and a substantial decrease postpartum. Decreasing serum levels of these hormones were associated with a trend in increasing uveitis activity.

In general, women with uveitis who become pregnant should be advised that their disease may flare during the first trimester or postpartum, and closer follow-up during these periods is advised.

Pregnancy-specific eye disease

Pregnancy-specific eye diseases include preeclampsia/eclampsia and cortical blindness.

Preeclampsia and eclampsia

Usually a disorder of first pregnancies, preeclampsia is characterized by hypertension (≥140 mm Hg systolic or ≥90 mm Hg diastolic) occurring after 20 weeks' gestation accompanied by proteinuria [23]. Preeclampsia is referred to as 'severe' when associated with a more significant elevation of blood pressure (≥160 mm Hg systolic or ≥110 mm Hg diastolic), more severe proteinuria, oliguria, pulmonary edema, abdominal pain, liver dysfunction, thrombocytopenia, or visual or cerebral abnormalities. Eclampsia is characterized by the development of tonic-clonic seizures in a preeclamptic patient.

Visual symptoms of preeclampsia and eclampsia include decreased vision, photopsia, and visual field defects [24]. Although abnormalities of the conjunctiva, retina and retinal vasculature, choroid, optic nerve, and visual cortex have been reported, the most common ocular finding is constriction of retinal arterioles [24–26], occurring in approximately 60% of patients with preeclampsia in one study [25]. The constriction may be generalized or localized [25,26]. If the constriction is severe, other changes associated with hypertensive retinopathy may occur, including retinal edema, hemorrhages, exudates, and cotton wool spots [26]. Exudative retinal detachment (ERD) has been reported in 0.1–32.4% of patients with preeclampsia [25,27,28]. Cortical blindness associated with pregnancy-induced hypertension is discussed in the next section.

Reports of angiographic findings in the literature are generally limited to postpartum studies performed to evaluate the cause of ERD and have supported the role of choroidal ischemia in ERD and other retinal changes observed in preeclampsia. Abnormal choroidal leakage and delayed filling of the choriocapillaris with normal retinal vasculature have been described [29], as has choroidal nonfilling [30]. On indocyanine green angiography, patients with preeclampsia demonstrate early choroidal nonperfusion and late staining of choroidal vessel walls [31].

Color flow Doppler ultrasonography of the central retinal artery performed during visual symptoms has demonstrated

a markedly elevated pulsatility index compatible with vasospasm [32]. Magnesium sulfate is recommended therapy for the prevention and treatment of seizures in patients with preeclampsia or eclampsia [23] and has been shown to significantly reduce the pulsatility index in the central retinal and posterior ciliary arteries [33].

The prognosis for patients with visual disturbance associated with preeclampsia is good [34]. Although ERD, retinal pigment epithelial lesions, or both were present in most eyes in a study of patients with severe preeclampsia or eclampsia, no patients had permanent visual loss [28].

The onset of photopsias or visual field defects in a pregnant patient cannot be taken lightly and may herald the onset of seizures. Such a patient should be seen first by an obstetrician to rule out preeclampsia, rather than by an ophthalmologist.

Cortical blindness

Cortical blindness is a rare but well known complication of preeclampsia/eclampsia, occurring in as many as 15% of cases [35]. It is characterized by vision loss in the face of normal pupil function and ophthalmoscopic examination and is caused by compromise of the occipital cortex. Cortical blindness usually resolves [36–41,42•,43], although symptomatic bilateral inferior scotomata [44] and asymptomatic visual field defects [45] have been reported to persist for several months postpartum. The duration of visual loss has been reported to range from 4 to 192 hours [35]. Cortical blindness has been described both before [36–38,41,42•,43] and after delivery [37,40]. Headache is commonly reported preceding or accompanying the visual disturbance [36–41,42•,43]. Visual disturbance has also been accompanied by hyperreflexia [42•,46••,47] and paresis [46••].

Computed tomography may demonstrate low-density lesions, often bilateral, in the occipital cortices [35,36, 38,39,44] or lesions in both occipital and parietal cortices [35,43]. Magnetic resonance imaging (MRI) demonstrates corresponding hyperintense lesions in the occipital cortex [36,39–41] or both occipital and parietal cortices [43,44] on T_2-weighted imaging. Although these findings on conventional computed tomography and MRI indicate the presence of cerebral edema, they do not elucidate the mechanism of edema formation.

The visual changes associated with preeclampsia/eclampsia and the corresponding changes on neuroimaging have been explained by two mechanisms. First, vasospasm, either generalized or localized, may cause transient ischemia, resulting in cytotoxic edema. Second, dysregulation of the posterior circulation, as may occur in severe hypertension, may result in increased vascular permeability, causing vasogenic edema. Recently, MRI diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping have been used in cases of preeclampsia/eclampsia in an attempt to differentiate vasogenic from cytotoxic edema [42•,46••,48]. The presence of both cytotoxic edema [42•,46••] and vasogenic edema [43] has been reported on DWI studies. In one of these studies finding cytotoxic edema [46••], magnetic resonance angiography (MRA) performed concurrently demonstrated diffuse vasospasm. Later studies revealed resolution of lesions on MRI and vasospasm on MRA. The authors concluded that neurologic dysfunction in preeclampsia/eclampsia is caused by progressive cerebral edema, vasogenic followed by cytotoxic, which may progress to infarction. The constellation of symptoms (headache, seizures, cortical blindness, and mental status changes) seen with hypertension associated with preeclampsia/eclampsia as well as other diseases is referred to as reversible posterior leukoencephalopathy syndrome [43,46••].

As acute visual changes associated with preeclampsia/eclampsia have been reported to occur prior to eclamptic seizures [37,47], visual loss should be considered a symptom of impending eclampsia in patients with preeclampsia [47].

Disease nonspecific to pregnancy: central serous chorioretinopathy

Central serous chorioretinopathy (CSCR) results from a localized serous detachment of the neurosensory retina in the macula. Although this condition is 10 times more common in men than women [49], it has a strong association with pregnancy [50]. A recent study confirmed this relation, finding an odds ratio of 7.1 in women with a previous or current pregnancy at time of examination versus their age-matched counterparts with no history of pregnancy [51•]. CSCR associated with pregnancy is more likely to cause subretinal fibrinous exudates, occurring in 75–100% of pregnant patients [52,53], compared with 17% of men and 0% of nonpregnant women [53].

Central serous chorioretinopathy typically resolves by 1–2 months after delivery [54]. Historically the diagnosis was based on clinical presentation, but a recent report showed the value of optical coherence tomography in diagnosing and following CSCR in pregnant patients. This technique allows visualization of the retina, subretinal space, and retinal pigment epithelium without the risks of exposure of the fetus to fluorescein dye [55•]. Fortunately, CSCR itself is not associated with adverse fetal outcomes.

Use of topical ophthalmic medications during pregnancy

Many medications are considered safe during pregnancy despite a lack of clinical trials involving pregnant women. A recent review article suggested that most topical ophthalmic drugs pose little risk to the mother and developing fetus [56••]. Despite this, caution should be exercised

when prescribing any ocular medication to pregnant women, especially drugs that are known to be dangerous when taken systemically.

Ocular hypotensives

Glaucoma medications are one example of medications that should be used cautiously during pregnancy.

The prostaglandin analogues, such as latanoprost, are category C drugs based on negative outcomes in pregnant animals exposed to high doses [57]. A recent study followed women who were exposed to the drug during the first trimester of pregnancy. They reported no adverse outcomes for the pregnancy or the newborns due to this exposure [58].

Acetazolamide has been associated with neonatal acidosis [59]. When this drug is used during pregnancy, levels should be monitored to prevent overdose and associated side effects [60].

β-Blockers are considered teratogens [61] and are typically not recommended during pregnancy. The β-blocker timolol has been associated with dangerous fetal cardiac arrhythmias in one report [62].

Topical steroids

Use of ophthalmic steroids is discouraged during pregnancy, but they obviously may be required to preserve vision in pregnant women with uveitis. In animal studies, topical steroids were found to be teratogenic [63], although preparations that are applied topically to human subjects have not been shown to cause birth defects.

As with any medication, it is important to weigh the risk versus benefit in using the drug. Ways to reduce systemic absorption, such as punctual occlusion, are discussed here and should be encouraged in pregnant patients.

Conclusion

Visual symptoms associated with diabetic retinopathy include blurring of vision, floaters, and partial or total vision loss. The symptoms may wax and wane, leading patients to believe that the condition is improving without treatment. Women need to be aware of these possible warning signs and advised to contact their ophthalmologist as soon as any visual changes are noticed. The benefit of routine ophthalmologic screening of pregnant diabetic patients cannot be overemphasized.

Women with uveitis who are pregnant or wish to become pregnant may be counseled that, although knowledge of the course of inflammatory eye disease during pregnancy is limited, the disease activity during pregnancy is not predicted by preconception activity. In general, uveitis may flare during the first trimester or postpartum. Women may also be counseled that corticosteroids are the only systemic drug routinely used to treat uveitis during pregnancy.

Acute onset of visual blurring, scotomata, and visual field defects may be a sign of severe preeclampsia or impending eclampsia. Frequently, visual symptoms are preceded or accompanied by severe headache. Pregnant patients presenting to the ophthalmologist with these symptoms, especially women with pregnancies greater than 20 weeks' gestation, require immediate referral to an obstetrician to be evaluated for preeclampsia. Similarly, an obstetrician faced with a pregnant patient with preeclampsia should be aware of the potential significance of acute visual symptoms.

Patients with CSCR may have blurred vision, central scotoma, metamorphopsia, and micropsia. Although the retinopathy typically resolves during the postpartum period, women who develop CSCR during pregnancy are at an increased risk of future recurrence [52].

Many women require ocular medications during pregnancy, and patients should be instructed on ways to decrease systemic absorption. Using the lowest possible dose of medication will reduce the total amount of drug available for absorption. Nasolacrimal compression and punctual occlusion help to reduce drainage of the medication through the nasolacrimal duct and absorption by the nasal mucosa [56••]. When prescribing topical ophthalmic medications, it is important to remember that the drugs will bypass the hepatic circulation involved in the metabolism of many orally administered drugs. Fetal exposure might also be longer in duration, as amniotic fluid is recirculated through the fetus. If a situation arises in which a systemic drug (e.g. for treatment of uveitis) or questionable topical drug is required, it is appropriate to consult an obstetrician before prescribing the medication.

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