Review Article

Pregnancy and diabetic retinopathy—considerations for evaluation and treatment: a review

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Abstract: The prevalence of diabetic retinopathy (DR) continues to increase in pregnant females; these individuals are also at a higher risk of disease progression. The lack of evidence regarding the safety and efficacy of current treatment options in pregnancy makes disease management particularly challenging. All pregnant women with diabetes should have a prenatal DR screening, as well as receive counseling regarding the progression and management of DR during pregnancy. Optimal blood glucose and blood pressure control should be encouraged. For patients with proliferative diabetic retinopathy (PDR) in the absence of visually significant diabetic macular edema (DME), panretinal photocoagulation (PRP) remains a safe and effective treatment option. Visually significant DME can be treated with focal laser if areas of focal leakage are identified in the macula on fluorescein angiogram, intravitreal steroids or anti-vascular endothelial growth factor (VEGF) agents, The theoretical risk of anti-VEGF agents to the fetus should be considered and the patients should be extensively counselled regarding the risks and benefits of initiating anti-VEGF therapy before initiating treatment. When the decision is made to treat with anti-VEGF agents, Ranibizumab should be the agent of choice. In conclusion, ophthalmologists should make treatment decisions in pregnant patients with DR on a case-by-case basis taking into consideration disease severity, risk of permanent threat to vision, gestational age, and patient preferences.

Keywords: Diabetic retinopathy (DR); pregnancy; laser photocoagulation; intravitreal steroids; anti-vascular endothelial growth factor

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Introduction

Background

The prevalence and progression of diabetic retinopathy (DR) in pregnancy remains higher than in the non-pregnant diabetic population (1), and these changes can persist for up to 12 months post-partum (2,3). The progression of DR during pregnancy is multifactorial and often a result of altered metabolic and hormonal states. In addition, rapid and tight metabolic control during pregnancy in women with previously poor metabolic control can also result in worsening of DR (4,5).

Rationale and knowledge gap

Management of DR during pregnancy poses several unique challenges; more aggressive disease and increased risk of progression during pregnancy, inability to administer anti-VEGF agents due to the possible maternal and fetal risks, and logistical difficulties caused by multiple medical appointments making disease control more difficult. In addition, well-designed clinical studies evaluating the safety

and efficacy of therapeutics used for treatment of DR in pregnant patients are lacking. Ethical issues surrounding enrollment of pregnant women in clinical trials has led to extrapolation of clinical evidence from studies in non-pregnant subjects which may not be applicable to pregnant patients.

Objective

Here we provide an overview of DR in pregnancy with a particular emphasis on considerations for evaluation and treatment of DR during pregnancy.

Prevalence and progression of DR during pregnancy

An increasing prevalence and younger onset of type 2 diabetes, in combination with increasing maternal age has led to an increase in the number of women with diabetes during pregnancy. The global prevalence of DR has been reported as 52.3% and 6.1% in pregnant patients with type 1 and type 2 diabetes mellitus (1). The rate for new DR development during pregnancy has been reported to be 15%, while progression from non-proliferative diabetic retinopathy (NPDR) to proliferative diabetic retinopathy (PDR) has been reported as 6.3% (1). The incidence of a new diagnosis of DR during pregnancy remains higher in patients with type 1 diabetes compared to type 2 diabetes (15.8% *vs.* 9.0%); however, the rate of progression of retinopathy remain similar between the two groups (1).

Risk factors for disease progression

Progression of DR during pregnancy; defined as deterioration of retinopathy by at-least 1 stage between serial fundus examinations has been associated with having Type 1 diabetes (6), baseline retinopathy status (7), longer duration of diabetes (8,9), poor glycemic control (10), preeclampsia/hypertension and pre-existing nephropathy (11,12). In addition, a greater drop in HbA1C and rapid tightening of glycemic control during pregnancy in women with poor metabolic control pre-pregnancy has also been associated with increased odds of DR progression (13,14).

Pre-pregnancy screening and disease monitoring

All pregnant women with diabetes should have a prenatal DR screening, as well as receive counseling regarding the progression and management of DR during pregnancy. The American Academy of Ophthalmology Preferred Practice Guidelines recommend screening for DR in the first trimester in diabetics and then every 3–12 months depending on DR severity. Patients with severe NPDR should be followed every 1–3 months (15). The American Diabetes Association recommends an eye exam in pregnant diabetics in the first trimester with close follow-up throughout pregnancy up to 1 year post-partum (16). The National Institute for Health and Care Excellence (NICE) guidelines recommend that pregnant women with pre-existing diabetes should have a retinal exam at the beginning of pregnancy and then again at week 28 if the first assessment was normal. If DR was present at the first exam, repeat follow-up examination should be performed between 16–20 weeks (17).

Prior to becoming pregnant women should be encouraged to optimize blood glucose and blood pressure control as it appears to be associated with decreased progression of DR (3,8). In unplanned pregnancies with poor glycemic control, optimal glycemic control should be prioritized as the risks in maternal and fetal outcomes associated with poor glycemic control during pregnancy outweigh the risks of DR progression as a result of prompt decrease in HBA1C (7,18). The intensive treatment in the Diabetes Control and Complications Trial (DCCT) showed that although early worsening of DR was noted in a higher proportion patient assigned to intensive treatment, the long-term benefits of tight glycemic control by far out-weight the risks associated with early disease worsening (13).

Role of multimodal imaging

Color fundus photography is helpful in documenting the severity of DR. The Early Treatment Diabetic Retinopathy Study (ETDRS) group initially defined stereoscopic color fundus photography in 7 standard fields (30°) as the gold standard method for detecting DR (19). More recently, wide-field fundus photography has been used with good correlation to seven standard color mydriatic fields (20). Optical coherence tomography (OCT) of the macula is a great tool to ascertain the presence and severity of diabetic macular edema (DME) and retinal structural changes due to ischemia (21,22). OCT has become the gold standard in diagnosing and following DME. Due to its reliability and repeatability has a higher accuracy than fundus

photography in the diagnosis of DME (23,24). Prior to the advent of OCT, clinicians would primarily rely on clinical exam characteristics to determine whether a patient had clinically significant macular edema (CSME) warranting treatment. Fluorescein angiography (FA) is considered the gold standard to assess for the degree of non-perfusion, macular ischemia, presence of neovascularization otherwise not appreciable on clinical exam, and can distinguish DME from other causes of macular edema (25). Widefield and ultra-widefield FA is especially advantageous in capturing non-perfusion and neovascularization, which often occur in the midperiphery and periphery and can be missed with traditional fundus photography. Ultra-widefield FA captures more non-perfusion and neovascularization than the standard seven-field image and is employed more often in current day management of DR (23).

Special considerations apply to pregnant patient with regards to FA and this imaging modality should only be employed in these patients where it is deemed to crucial for clinical management and decision making. For example, in cases of unexplained visual loss or when the etiology of neovascularization or macular edema may be uncertain. Studies have shown that the fluorescein dye can cross the placenta and enter the fetal circulation (26), although no dye related adverse effects on fetal well-being have been documented (27). Pregnant patients should be provided with all the relevant information and informed decision making should be encouraged before proceeding with a fluorescein angiogram. Fluorescein dye can also be present in breast milk for up to 72 hours after dye injection; this information should be made available to breast feeding mothers (28). Optical coherence tomography angiography (OCTA) can serve as a valuable alternative imaging modality to assess microvascular changes and retinal non-perfusion in pregnant and nursing women (29). OCTA has the capability to visualize distinct retinal vascular layers with high axial resolution. Studies have shown several quantitative OCTA measures correlated to severity of DR, including reduced vessel density in the superficial and deep capillary plexuses, increased foveal avascular zone, and the presence of microaneurysms (30-32). While there is a promising role for OCTA as a technique for monitoring DR disease progression, there are some important limitations including the propensity for artifacts and segmentation errors with this modality, the limited field of view, and inability to assess the retinal periphery and vascular leakage (33).

Medical and surgical management

Observation

Patients with mild to moderate NPDR and those with mild to moderate DME can be managed conservatively with close observation and optimal blood glucose and blood pressure control; this alone at times can result in significant disease stabilization (34). The severity of DR at conception is important to guiding management in these patients as progression of DR in pregnancy has been shown to be more significant in pregnant patients with moderate and severe forms of DR compared to those with mild or no DR at conception. In fact, in the Diabetes in Early Pregnancy Study, 55% of pregnant women with moderate to severe NPDR worsened while only 21% of those with mild NPDR progressed (10). Of course, each patient needs to be closely observed and monitored for progression. Risk factors for progression also need to be assessed including duration and control of diabetes, concurrent hypertension, dyslipidemia, and nephropathy (35). In patient with disease progression, treatment modalities described below can be used on a case-by-case basis.

Treatment considerations for DME

Treatment options for DME vary based on the patient's vision, disease severity and imaging findings. In general, a stepwise approach is recommended in DME treatment. If there is no central involvement (within the central 1 mm) on OCT, treatment is deferred and tight glycemic and blood pressure control recommended (36). Additionally, based on Protocol V, patients with vision better than 20/30 and center-involving DME can be observed (37). In patients with center-involving DME and vision worse than 20/30 treatment should be considered. In non-pregnant patients, on the basis of studies by the DRCR.net, anti-VEGF agents are generally the first-line of treatment (38). However, below we discuss treatments that may be considered in pregnant patients due to the risks of anti-VEGF during pregnancy.

Focal laser

Focal laser is often the treatment of choice employed by retina specialists for macular edema in pregnancy (39). It is the ideal treatment choice when macular edema is caused by leaking microaneurysms away from the fovea; these

microaneurysms can be easily targeted by focal laser leading to resolution of macular edema. In fact, modified focal laser can be superior to intravitreal steroids and is a durable treatment option (40,41). However, when microaneurysms are close to the fovea or when macular edema is the result of diffuse vascular leakage rather than leaking microaneurysms, or in patients with refractory macular edema despite focal laser, alternate treatment options need to be explored.

Intravitreal steroid therapy

In pregnant patients who are not good candidates for focal laser, intravitreal steroids remain a safe and effective treatment option (42). Three potential intravitreal corticosteroid treatments may be employed: triamcinolone acetonide, dexamethasone, and fluocinolone acetonide. Case reports employing triamcinolone acetonide have shown improvement in visual acuity without adverse events (43). Similar favorable visual and anatomical outcomes have been reported in 8 eyes of 5 pregnant patients with fovea involving DME treated with dexamethasone intravitreal implant without significant intraocular pressure increase (44). Intravitreal steroids remain a reasonable treatment option in patients with visually significant DME. They may be a preferred treatment option in pregnancy, when treatment with anti-VEGF therapy is not desirable.

Role of anti-VEGF therapy

Based on studies by the DRCR.net anti-VEGF agents are the first-line treatment for DME in non-pregnant patients (45). However, the use of anti-VEGF agents in pregnancy is controversial given the risk of potential fetal harm. In most cases, anti-VEGF agents are only considered in pregnancy as the last resort given the lack of long-term safety data and administration is preferred in the third trimester (46).

Animal studies with anti-VEGF agents administered at a higher dose than what is recommended in humans has been associated with the risk of fetal abnormalities (47,48). There are no adequate and well-controlled studies in humans and evidence regarding the adverse effect of anti-VEGF therapy on fetal and maternal health during pregnancy is limited. As VEGF has been postulated to play a role in the normal development of fetal and placental vasculature (49,50), its reduced levels have been thought to result in possible teratogenicity.

The blood levels of VEGF have been showed to be decreased after a single intravitreal injection of anti-VEGF agents in humans (51), however anti-VEGF agents are not known to cross the placental barrier and it is possible that fetal VEGF levels remain fairly stable despite changes in maternal VEGF levels. However, testing fetal VEGF levels remains challenging in a clinical setting and therefore the effects of intravitreal anti-VEGF agents on fetal VEGF levels are largely unknown.

Decision on the type of anti-VEGF is largely dictated by the drug half-life in the plasma. Bevacizumab remains in the plasma much longer and it has been observed that an intravitreal dose of bevacizumab could reduce plasma VEGF levels for at least one month. The shorter half-life and rapid plasma clearance of Ranibizumab makes it the potential agent of choice in pregnant patients and in patients who are anticipating to get pregnant shortly after their anti-VEGF treatment (52,53). It is recommended that women wait for at least 3 months after their last anti-VEGF injection prior to conceiving.

Despite the concerns surrounding the potentially harmful effects of anti-VEGF agents during pregnancy, there are a few reported cases suggesting the safe use of anti-VEGF agents in early un-diagnosed pregnancy without any adverse maternal or fetal outcomes (46,54,55). Given the lack of strong evidence regarding the safety of anti-VEGF agents in pregnancy, retina specialists may consider alternate treatment modalities prior to considering the use of anti-VEGF agents for the treatment of DME in pregnancy. This decision should be individualized to each patient after a thorough evaluation and discussion of risks and benefits. Watchful waiting may be appropriate on a case-by-case basis. Studies have shown similar visual acuity outcomes in patients with DME where anti-VEGF treatment had been delayed by 12 months versus those who received prompt treatment at the 36 months follow-up (56). In addition, DME may resolve spontaneously following delivery in a subset of patients, making watchful observation a reasonable management option for DME in pregnancy.

Panretinal photocoagulation (PRP)

PRP is a safe treatment option in pregnant patients with DR and remains the mainstay in preventing disease progression (57). Treatment with PRP is warranted at an earlier stage in pregnant patients with recommendations to treat when level of DR is severe NPDR or worse (58-60). In patients with pre-existing DME, careful decision making must be employed with regards to need for treatment, as

well as timing and intensity of treatment as PRP carries the risk of worsening DME. This is particularly relevant in pregnant patients as there is a lack of evidence on the safety and efficacy of anti-VEGF therapy in pregnancy.

Surgical treatment options

Certain complications related to DR might warrant surgical intervention. The most common indications for surgery in diabetic patients include non-clearing vitreous hemorrhage, vision threatening tractional retinal detachments, and neovascular glaucoma (61). However, surgical planning is often more difficult in pregnant patients due to factors influenced by patients ability to position supine during the surgery, maternal and fetal risks associated with anesthesia and the burden of post-operative care including frequent clinic visits. Decision for surgery should be made on an individual basis, taking into account gestational age, the status of the fellow eye, and risk for permanent vision loss. Any surgery should be planned in conjunction with the patient's obstetrician as these patients often require fetal monitoring during surgery and local anesthesia is preferable to general anesthesia as general anesthesia is associated with increased maternal (risk of deep venous thrombosis, pulmonary embolism, aspiration etc.) and fetal complications (spontaneous abortion and pre-term labor) (62). In general and if possible, surgery should be delayed until the third trimester or following delivery.

Delivery and post-partum care

At present, there is no strong evidence to dictate mode of delivery in patients with DR. Some studies suggest an increased risk of Valsalva induced vitreous hemorrhage in patients with PDR (63). The mode of delivery ultimately should be dictated by factors which lead to best maternal and fetal outcomes and DR status should not be considered a contraindication to vaginal delivery.

In pregnant patients with diabetes, retinopathy may progress more rapidly than in patients who are not pregnant. Improving glycemic control before pregnancy and early examination in the first trimester is important to determining follow-up intervals and guiding treatment (15). In some patients the pregnancy associated effects on the retinal microvasculature may be transient and resolve 6–12 months after delivery, with risk of progression returning to pre-pregnancy level after 1 year as shown by the Pittsburg study in the Epidemiology and Complications of Diabetes (18). In these patients careful monitoring is appropriate as long as there are no vision-threatening complications. Interestingly, although DR does worsen during pregnancy, studies including the Diabetes Control and Complications trial have shown that pregnancy has no long-term effect on future disease progression (64-66). Patients with DR should be monitored closely during the post-partum period with serial examinations, the frequency for which should be determined by DR severity (18). Patients without retinopathy or with mild to moderate NPDR should be examined every three to six months and those with severe NPDR every one to three months.

Conclusions

In the prenatal period women should be appropriately counselled regarding the effect of pregnancy on DR and optimal glycemic control should be encouraged. Screening eye examination should be performed prior to being pregnant or in the first trimester and again through the duration of the pregnancy and post-partum period depending on the severity of the DR. PDR should be treated with panretinal laser photocoagulation. Focal laser, when the disease is amenable to this treatment option, or intravitreal steroids are the preferred treatment options for DME in pregnancy. When decision is made to treat with anti-VEGF agents, Ranibizumab remains the agent of choice given its shorter half-life and faster plasma clearance. Watchful waiting may also be employed in many cases of mild to moderate DME as prior studies have shown similar outcomes in those patients receiving prompt versus delayed treatment for DME.

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