

# Diabetes Mellitus: A Non Systematic Evidence Based Review

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**W**orld-wide it is estimated that over 2.5 million people are blind due to diabetes mellitus. The exact pathogenesis of diabetic retinopathy is not fully understood.

Some factors may act simultaneously in the pathogenesis diabetic retinopathy. Although major advances in the clinical diagnosis and treatment of diabetic retinopathy and its associated complications have been achieved over the past 5 decades, diabetic retinopathy remains the leading cause of new blindness among working-age individuals in developed countries. Understanding the risk factors that may lead to progression among diabetic women in pregnancy is of great important in the management of diabetic retinopathy. Patients who are in good glucose control at the start of pregnancy and who maintain tight control during pregnancy have little risk of progression of retinopathy. Slowing the progression of retinopathy and reducing visual loss in pregnancy seems to be by the use of laser photocoagulation before pregnancy

**Key Words:** Diabetic Retinopathy, Pregnancy, Type 1 Diabetes Mellitus

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## Introduction

Over 2.5 million people worldwide suffer from blindness due to diabetes mellitus, the

fourth leading cause of world blindness and an ever increasing problem in developing nations. Although major advances in the clinical diagnosis and treatment of diabetic retinopathy and its associated complications have been achieved over the past 5 decades, diabetic retinopathy remains the leading cause of new blindness among working-age individuals (20-65 years), coinciding with peak fertility and childbearing years, individuals in developed countries.<sup>1-4</sup> In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% of type 1 diabetics and 1.6% of type 2 diabetics were legally blind.<sup>5,6</sup> The most frequent ocular complication of diabetes mellitus is diabetic retinopathy.<sup>1,3,4,7-10</sup> Approximately 25% of patients with type 1 diabetes have some form of retinopathy 5 years after the onset of diabetes; after 10 years of having diabetes, more than 70% of these patients have retinopathy; 97.5% have retinopathy if they have had diabetes for 15 years or longer. Proliferative diabetic retinopathy, the most vision-threatening form of the disease, is present in approximately 25% of patients who have had type 1 diabetes for 15 years. Up to 3% of patients with diabetes first diagnosed after age 30 can have clinically significant macular edema or vision-threatening proliferative dis-

ease at the time of the initial diagnosis of diabetes.<sup>5,6,11</sup> The WESDR estimated that 26% of patients with early onset and 36% of patients with onset after age 30 had not been examined by an ophthalmologist in the preceding 2 years. In this population, 11% of type 1 diabetes and 7% of type 2 diabetes patients with proliferative retinopathy, the vision-threatening form of retinopathy, had not been seen by an ophthalmologist within the last 2 years.<sup>12</sup> Also, more than 50% of the patients with proliferative retinopathy had never had laser treatment.<sup>13</sup> Understanding the risk factors that may lead to progression among women with diabetes in pregnancy is of great importance in the management of diabetic retinopathy. Rapid lowering of elevated glucose levels is recommended during pregnancy for optimal fetal development,<sup>14</sup> but it is worrying if it is associated with a risk of progression of retinopathy in the mother. The reported prevalence of diabetic retinopathy during pregnancy varies from 14 to 85%,<sup>15,16-28</sup> however, some other reports found no correlation.<sup>29-31</sup> The natural history of diabetic retinopathy and the interventions that may be used in the various stages of the disease have been examined in major trials like the Diabetic Retinopathy Study,<sup>32-33</sup> the Early Treatment Diabetic Retinopathy Study,<sup>34</sup> and the Diabetic Retinopathy Vitrectomy Study.<sup>35</sup> There has been controversy as to whether the progression of retinopathy is due to the natural tendency of diabetic retinopathy to worsen or to unique factors operative during pregnancy. Some patients do have further deterioration of their retinopathy postpartum<sup>27,36</sup>

## Material and Methods

**Clinical spectrum:** The spectrum of diabetic retinopathy extends from nonproliferative diabetic retinopathy including retinal microaneurysm, the first lesion of diabetic retinopathy found in 98% of individuals with type 1 diabetes who have had diabetes for 15 years or more, dot or blot hemorrhages resulting from extravasation of blood from

retinal capillaries into the inner nuclear layer of the retina and hard exudates collections of lipoproteins that leak from microaneurysms into the outer retinal layer, which may also accompany macular edema, cotton-wool infarcts, venous loops and beading and intraretinal microvascular abnormalities, to proliferative diabetic retinopathy marked by the growth of abnormal blood vessels (neovascularization) which is stimulated by retinal ischemia.<sup>37</sup> The retinal vessels may become abnormally permeable at any stage in the disease process. This abnormal permeability results in transudation of blood serum components into the retina and a thickening of the retina called macular edema. When this edema involves or threatens the center of the macula, it is called clinically significant macular edema and it can result in visual loss. There are two main risks of neovascularization as they are prone to rupture causing bleeding (vitreous hemorrhage) or when they become mature may lead to contraction (retinal detachment).

**Pathogenesis:** The exact pathogenesis of diabetic retinopathy is not fully understood, however, some or all of these factors may act simultaneously in the pathogenesis diabetic retinopathy.

**Hyperglycemia:** Hyperglycemia leads to increased cell uptake of glucose with deleterious effects which may be mediated by several mechanisms, including accumulation of sorbitol, nonenzymatic glycation of proteins, and local production of vasoproliferative factors.

**Sorbitol:** Aldose reductase is an enzyme that converts glucose to sorbitol. It is the first enzyme in the polyol pathway, a series of enzymatic reactions in the synthesis of fructose. Normally, aldose reductase has a low affinity for glucose and little glucose substrate enters the polyol pathway; during hyperglycemia, however, cellular levels of glucose increase, particularly in tissues such as the retina where glucose entry is independent of insulin. The excess glucose is largely metabolized by aldose reductase, and this increased

flux of glucose through the polyol pathway is associated with diabetic abnormalities.

**Advanced glycation end products:** Extracellular glucose may react with primary amino acids in a non-enzymatic process forming advanced glycation end products (AGEs). AGEs are irreversibly chemically damaged proteins, and in animal models the levels increase in vascular tissue within a few weeks of the induction of diabetes and may exacerbate the pathogenetic processes of late complications.<sup>38</sup>

**Autoregulation:** Loss of autoregulation i.e. a loss of the capacity to maintain constant flow despite a change in pressure head appears to be one of the characteristic of diabetic microcirculation.<sup>39</sup> The blue field entoptic technique was used to study autoregulation of the macular retinal circulation in response to acute alterations of intraocular pressure in 71 diabetic eyes. When compared with normal control subjects, diabetic patients with retinopathy appear unable to maintain the same constancy of capillary flow velocity in the face of intraocular pressure.<sup>40</sup> Using laser doppler velocimetry which measures blood flow in the major retinal veins, Grunwald et al found a reduction in volume flow and increase in the retinal vessels autoregulatory response to 100% oxygen.<sup>41</sup> In contrast, a study by Davies of 20 poorly controlled type 1 diabetic patients using the blue light entoptic technique failed to show a significant change in flow velocity or vessels diameter with normalization of plasma glucose values, consistent with a previous report.<sup>42,43</sup> The discrepancy between these results have been postulated to the different retinal vessels measured, the difference in response of the macula and peripheral retina to hypoxia and the patients studied being different in degree of severity of retinopathy.

**Protein kinase C and Endothelins:** Hyperglycaemia activates the Protein Kinase C signal pathway. This pathway regulates permeability, contractility, cell growth and angiogenesis in vascular cells. PKC affects the activation of a number of growth factors and

change the expression or function of vasoactive factors like endothelin-1 and nitric oxide.<sup>44,45</sup> Alteration of endothelins are important in several vascular dysfunction.<sup>46</sup> Best et al found significantly higher levels of plasma endothelin-1 in 13 pregnant women with type 1 diabetes through out the pregnancy trimesters as compared with those without diabetes.<sup>47</sup> However, this study showed that there was no difference in endothelin-1 levels between those with or without retinopathy.

**Growth factors:** Poor metabolic control in type 1 diabetes changes the expression of several growth factors and their local effects, such as IGF-I, transforming growth factor (TGF) and vascular endothelial growth factor (VEGF).<sup>48</sup> IGF-I and VEGF are the two main growth factors which may play a role in retinal microcirculation. IGF-1 receptor regulation of VEGF action is mediated, at least in part, through control of VEGF activation of protein kinase, establishing a relationship between IGF-1 and VEGF receptors. IGF-1 has an essential role in angiogenesis and demonstrated a new target for control of retinopathy. Diabetic retinopathy initially increases with the onset of insulin treatment as IGF-1 levels, low in untreated diabetes and rises with insulin therapy, permitting VEGF-induced retinopathy.<sup>49</sup> Vascular endothelial growth factor (VEGF) is an endothelial cell-specific angiogenic and permeability-inducing factor that has been implicated in the pathogenesis of diabetic retinopathy.<sup>50</sup> Fibroblast growth factor-2 is a potent mitogen and angiogenic factor normally absent from the adult circulation and found in pregnant women with type 1 diabetes.<sup>51</sup>

**Serum hormone levels:** During pregnancy, there is marked change in serum patterns of some steroid and protein hormones. Larinkari et al studied 57 pregnant women with type 1 diabetes and find the serum concentration of progesterone and human placental lactogen to be significantly increased in women with diabetes during the last trimester compared with those in normal preg-

nancies, and during the second trimester, patients with retinopathy showed significantly higher concentrations than those without, but no significant difference was found in estradiol level; no correlations was found between serum prolactin values and occurrence of retinopathy.<sup>52</sup>

**Genetic factors:** The effect of genetic factors on the development of retinopathy is not well understood; while Dornan et al found an increased frequency of the HLA-DR4 gene among patients with nonproliferative diabetic retinopathy (background) and proliferative retinopathy,<sup>53</sup> others could not find the same correlation.<sup>54</sup> The DCCT research group investigating 372 patients found that severe retinopathy was three times more frequent among the relatives of the retinopathy-positive patients than the retinopathy-negative patients.<sup>55</sup>

### Risk factors

**Glycemic control:** Glucose control has been shown to affect the risk of progression of retinopathy in type 1 diabetic pregnancies. Both an elevated initial HbA1c and the magnitude of improvement in HbA1c have been reported to be predictors of progression.<sup>15-17,24,27,56</sup> It has been difficult to separate the effects of a high initial HbA1c from the magnitude of the decrease since patients with the highest values are those who are likely to experience the largest drop. Rapid lowering of elevated glucose levels is recommended during pregnancy for optimal fetal development,<sup>14</sup> but it is worrying if this is associated with a risk of progression of retinopathy in the mothers. A study conducted on normal cats found that the retinovascular response to glucose infusion suggests a breakdown in the normal response of tissue autoregulation.<sup>57</sup> Although elevated blood glucose levels are associated with decreased retinal arterial regulatory responses which could play a role in the development of diabetic retinopathy,<sup>40,58</sup> gradual decrease in blood glucose may be beneficial.<sup>41</sup> In one study, short term fluctuations in plasma glucose levels were

not associated with hemodynamic changes in the macular capillaries of patients with established retinopathy.<sup>42</sup> We performed a retrospective analysis of the relation between glucose control and fluctuation and the progression of retinopathy during pregnancy as assessed by colour stereoscopic fundus photographs in 49 pairs of photographs. Higher initial HbA1c ( $0.070 \pm 0.01$  vs  $0.062 \pm 0.011$ ,  $p=0.02$ ) but not the degree of improvement in HbA1c or the daily capillary glucose values, were associated with a risk of progression.<sup>28</sup> Initial HbA1c of .070 is the lowest reported<sup>17,24,56</sup> to be associated with an increased risk of retinopathy progression, indicating that even mildly elevated glucose levels may result in an increased risk to the mother as well as the fetus. While pre pregnancy care with achievement of optimal glucose control is recommended, it is not accomplished in most women.<sup>14,59</sup> The Diabetes in Early Pregnancy Study, a prospective cohort study of 140 pregnant diabetic women who were followed from early pregnancy to delivery using retinal photography, has shown that those women with the greatest reduction in HbA1c over the first 14 weeks of pregnancy were at an increased risk of progression of retinopathy. Patients in whom retinopathy was most likely to progress had both the poorest control at baseline and the largest improvement during early pregnancy. However, the study could not analyze the relative contributions since the measures were highly correlated and all patients improved.<sup>17</sup> Rosenn et al<sup>24</sup> performed a multivariate analysis and found no independently additive effect of the initial HbA1c and the magnitude of decrease on the risk of progression of retinopathy. Some studies did not report a separate analysis.<sup>56</sup> However, initiation of intense insulin therapy in nonpregnant patients is well known to carry a risk of early worsening of retinopathy.<sup>60,61,62</sup> In the DCCT, the magnitude of the drop in HbA1c was more important than the initial value or the absolute value after six months of treatment in predicting the risk of progression.<sup>60</sup> These

studies confirmed our recommendation that patients who are in good glucose control at the start of pregnancy and who maintain tight control during pregnancy have little risk of progression of retinopathy.

**Duration of diabetes:** Diabetes duration has been found to be correlated inversely with progression of retinopathy in pregnant women.<sup>19,24,26</sup> Although structural changes in the retina may be found shortly after the diagnosis of diabetes, they are usually not reproducible. Diabetic retinopathy lesions may improve and fluctuate or wax and wane. The Wisconsin Epidemiologic Study of Diabetic Retinopathy is a population-based study in southern Wisconsin of 996 insulin-taking diabetics. The prevalence of diabetic retinopathy varied from 17% to 97.5% in persons with diabetes for less than five years and 15 or more years, respectively. Proliferative retinopathy varied from 1.2% to 67% in persons with diabetes for less than ten years and 35 or more years, respectively. The EURODIAB Prospective Complications Study includes the largest cohort so far of 3250 patients with Type I diabetes metabolic control and duration of diabetes are strong indicators of progression to proliferative retinopathy found the standardized regression estimate of diabetes duration (1.71, CI 1.42-2.06).<sup>63</sup> Davies et al<sup>42</sup> suggested that short term fluctuations in plasma glucose levels are not associated with hemodynamic changes in the macular capillaries in patients who have established retinopathy in 20 non-pregnant poorly controlled type 1 diabetic patients (18.5±7 years). A mechanism has been suggested by Grunwald et al<sup>41</sup> in study of poorly controlled type 2 patients (diabetes duration 7.3±5 years) by using laser doppler velocimetry which measures blood flow in the major retinal arteries and veins, that decrease in volume flow accompanying the insulin induced drop in blood glucose levels correlated significantly with the patient's duration of diabetes; the shorter the diabetes duration, the large in the decrease in flow. These findings indicate that duration of diabetes may be a

significant factor in the development of diabetic retinopathy.

**Blood pressure:** It is well established that hypertension is an independent risk factor for diabetic retinopathy.<sup>24,64</sup> Hypertension may complicate diabetes in that it may result in hypertensive retinal vascular changes superimposed on the preexisting diabetic retinopathy further compromising retinal blood flow. A prospective evaluation of 1109 patients showed 43.2% had proliferative retinopathy, 21.5% had maculopathy, 7% had both, 7% had preproliferative retinopathy, 16.5% had nonproliferative diabetic retinopathy, 3.2% had advanced retinopathy, and 1.3% had no retinopathy. There were significant differences among groups for all measures except intraocular pressure when evaluating different grades of retinopathy. Systolic blood pressure and retinal perfusion pressure were significantly elevated in patients with sight-threatening retinopathy.<sup>65</sup> Rosenn et al prospectively followed one hundred fifty-four women type 1 diabetics; fifty-one women had progression of retinopathy during pregnancy where chronic hypertension, and pregnancy-induced hypertension were significantly associated with progression of retinopathy.<sup>24</sup> In a prospective study by Lauszus of 112 pregnant women with type 1 diabetes, no association was found between progression of retinopathy and 24-hour blood pressure. In sixty-five pregnant Type 1 diabetic women, those patients who developed pre-eclampsia during pregnancy, deterioration of retinopathy occurred more frequently compared to those without pre-eclampsia.<sup>56</sup> Healthy young subjects in whom retinal white blood cell flux was measured with the blue-field entoptic technique and blood flow velocity in the central retinal artery was measured by means of color Doppler imaging. Retinal white blood cell flux and mean flow velocity in the central retinal artery were significantly associated with mean arterial pressure.<sup>66</sup> A 10-mmHg increase in systolic blood pressure was significantly associated with incidence of retinopathy in subjects

with younger-onset diabetes, 10 years after the baseline examination.<sup>67</sup> In the WESDR cohort, an elevated pulse rate was associated with 4 year progression of diabetic retinopathy. However, these associations became statistically non-significant after controlling for known retinopathy risk factors.<sup>5,6</sup> However, in a subsequent paper by the same study group, they found that pulse rate may be a clinical indicator of overall risk of diabetic retinopathy, but is not independently associated with the condition.<sup>68</sup> These findings suggest monitoring and control of blood pressure during pregnancy is a valuable risk factor of diabetic retinopathy.

**Baseline severity of retinopathy:** In the Diabetes in Early Pregnancy Study, A prospective cohort study of 155 diabetic women followed from the periconceptional period to 1 month postpartum found that progression of retinopathy was seen with no retinopathy, microaneurysms only, mild nonproliferative retinopathy, and moderate-to-severe nonproliferative retinopathy at baseline in 10.3, 21.1, 18.8, and 54.8% of patients, and proliferative retinopathy developed in 6.3% with mild and 29% with moderate-to-severe baseline retinopathy.<sup>17</sup> In sixty-five patients who were pregnant and had type 1 diabetes, progression of the retinopathy occurred in 77.5% of patients who presented with diabetic retinopathy at conception; proliferative diabetic retinopathy occurred in 22.5%. Only 26% of the patients who started the pregnancy without diabetic retinopathy had some progression of the retinopathy.<sup>26</sup> These findings indicate that severity of existing diabetic retinopathy profoundly influences the level of progression.

**Effect of pregnancy on diabetic retinopathy:** Whether pregnancy influences the development of retinopathy or the progression of established retinopathy remains controversial.<sup>18-23,27,29</sup> The Diabetes Control and Complications Trial (DCCT), a multicenter controlled clinical trial that compared intensive treatment with conventional diabetes therapy that studied 180 women who had had 270

pregnancies and 500 women who did not become pregnant during an average of 6.5 years of follow-up. Compared with nonpregnant women, the pregnant ones women had a significant 1.63-fold risk of worsening of retinopathy from before to during pregnancy in the intensive treatment group; in the conventional group, the risk was 2.48-fold for pregnant vs. not pregnant women.<sup>27</sup> Schocket et al used bidirectional laser doppler velocimetry and monochromatic fundus photography to assess the retinal circulation in seven pregnant diabetic patients and 13 age-matched pregnant control subjects in whom there was a significantly greater decrease in the retinal venous diameter in diabetic than in nondiabetic mothers during the third trimester and a reduction in retinal volumetric blood flow in diabetic patients during pregnancy that was significantly larger than in nondiabetic women; this may exacerbate retinal ischemia and hypoxia associated with the progression of diabetic retinopathy.<sup>69</sup> A prospective study by Klein et al in diabetic retinopathy in insulin-taking pregnant or nonpregnant diabetic women found that after adjusting for glycosylated hemoglobin, the current pregnancy was significantly associated with progression (adjusted odds ratio 2.3).<sup>16</sup> A prospective study including 22 women diabetics with or without moderate nonproliferative diabetic retinopathy using fluorescein angiography showed that the mean number of microaneurysms increased from 42.7 before pregnancy to 56.7 at the 28th week and to 79.7 at the 35th week.<sup>22</sup> Moloney et al in a study of 53 diabetic women and 39 nonpregnant type 1 diabetes of childbearing age (controls matched for age, duration of diabetes and basal insulin requirement to that of the 53 pregnant women), reported 62% had retinopathy at the first examination and 15% developed it as pregnancy advanced, significantly increasing the prevalence of retinopathy during pregnancy to 77.4%; microaneurysms moderately increased, hemorrhages appeared in 56.6%, and soft exudates in 28.3% and 7.5% had neovascularization.<sup>20</sup>

These changes regressed six months after delivery. However, The EURODIAB study examined 776 nulliparous and 582 parous women with Type 1 diabetes from a cross-sectional study performed in 31 European centres showed that the equivalent level of nonproliferative diabetic retinopathy in parous and nulliparous women suggests that pregnancy may not exacerbate these early complications.<sup>70</sup> Although the major determinants of progression of diabetic retinopathy during pregnancy were not clearly defined, many of the progressive changes in diabetic retinopathy during pregnancy appeared to be reversible.

**Microalbuminuria:** Prospective studies focusing on the relationship between diabetic retinopathy and the presence of microalbuminuria in pregnancy are lacking. The Wisconsin Epidemiologic Study of Diabetic Retinopathy of 1139 patients after controlling for glycemia, hypertension, and duration of diabetes found that younger-onset (diagnosed with diabetes before 30 years of age) and older-onset individuals with microalbuminuria were more likely to have retinopathy than those without microalbuminuria and were more likely to have proliferative retinopathy.<sup>71</sup> In 982 patients with type 1 diabetes, the prevalence of proliferative retinopathy and blindness rose with increasing albuminuria, being 12% and 1.4%, respectively, in patients with normoalbuminuria, 28% and 5.6% in those with microalbuminuria and 58% and 10.6% in those with macroalbuminuria.<sup>72</sup> A study of 86 patients of type 1 diabetes found that the prevalence of microalbuminuria was significantly higher in the proliferative retinopathy group compared to the group without retinopathy and the nonproliferative diabetic retinopathy group and that the frequency of diabetic retinopathy was significantly higher in patients with than those without microalbuminuria.<sup>73</sup> Gilbert et al in a longitudinal study of eighty patients with type I diabetes in the absence of any differences in long-term glycemic control or duration of diabetes found that proliferative retinopathy

developed in 62% of patients with evolving nephropathy compared with five of 7% of patients who were persistently normoalbuminuric.<sup>74</sup> Based on these findings, the presence of microalbuminuria prompts us to be on the vigil more frequently for diabetic retinopathy and changes that may occur.

**Gravidity:** Klein et al performed a population-based sample of 397 women with diabetes; 197 had never been pregnant, 88 had been pregnant once, 56 had been pregnant twice, and 56 had been pregnant three or more times after diabetes was diagnosed. The number of pregnancies was positively associated with the severity of retinopathy. However, this relationship was no longer apparent after controlling for duration of diabetes.<sup>75</sup> Vaarasmaki et al found that retinopathy was aggravated most often during the first pregnancy and occurred infrequently in the second pregnancy.<sup>76</sup> It seems that gravidity has no impact on the progression of diabetic retinopathy in pregnancy.

**Effect of diabetic retinopathy on pregnancy:** In small studies, adverse outcomes in pregnancy have found to be related to the severity of diabetic retinopathy. Reece et al included twenty pregnancies complicated by advanced diabetic retinopathy in a retrospective study; spontaneous abortion occurred in 10% and stillbirth in 5% with a mean birth weight of 2,620 g. The perinatal survival rate was 94%. Photocoagulation therapy was necessary prior to pregnancy in 45%, during pregnancy in 60%.<sup>77</sup> Price et al retrospectively reviewed 23 pregnancies in type 1 diabetes. They noted that 30% of patients who had no observable retinopathy and 70% of patients with nonproliferative diabetic retinopathy at inception of pregnancy developed obstetric complications.<sup>78</sup> Klein et al evaluated 179 pregnant diabetic women in their first trimester of pregnancy, 43% of the women with proliferative retinopathy had unfavourable pregnancies as compared with 13% of those to non-proliferative or no retinopathy and a fifth of the pregnancies resulted in fetuses with severe congenital mal-

formations and/or fetal death.<sup>79</sup> In a prospective study of diabetes in pregnancy McElvy, et al studied 250 women with type 1 diabetes before 14 weeks gestation, who were treated with intensive insulin therapy, and found that reduced fetal growth was associated with progression of retinopathy; mean birth weight was lower and more infants were small for gestational age.<sup>80</sup>

**Management of diabetic retinopathy in pregnancy:** Because of the substantial risk of severe visual loss, advanced diabetic retinopathy and proliferative retinopathy were considered a contraindication to pregnancy and women with diabetes who became pregnant were advised to consider termination.<sup>81</sup> This belief was changed after establishment and recognition of high risk characteristics and use of laser photocoagulation which reduced the likelihood of visual loss.<sup>82</sup> One of the key methods used to slow the progression of retinopathy and reduce visual loss in pregnancy seems to be laser photocoagulation before pregnancy. However, there are a group of women in whom retinopathy is aggressive, responds poorly to photocoagulation, and continues to progress postpartum. Thus, it is important that proliferative retinopathy is detected and treated preferably before the onset of pregnancy.<sup>83</sup> A study of patients with proliferative retinopathy detected

in early pregnancy and subsequently treated by laser showed that 58% experienced significant progression and visual loss and 26% of patients in whom retinopathy was diagnosed and treated before onset of pregnancy showed progression.<sup>84</sup> When planning pregnancy, women with preexisting diabetes should have a comprehensive eye examination and should be counseled on the risks of development and/or progression of diabetic retinopathy. Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and close follow-up throughout pregnancy.<sup>85</sup> While pre-pregnancy care with achievement of optimal glucose control is recommended, this is not accomplished in most women.<sup>14,59</sup> Diabetic retinopathy may be worsen after the institution of strict glycaemic control, however, there is an overall strong beneficial effect which includes a reduction of retinopathy by 50% at 2 years of follow up and the success of outcome of pregnancy in diabetes.<sup>62</sup> Recommendations as supported by the Diabetes in Early Pregnancy Study that suboptimally controlled diabetic women contemplating pregnancy, should be targeted for the institution of strict glycemic control.<sup>17</sup>

In summary, understanding the risk factors that may lead to progression of retinopathy among diabetic women during pregnancy is of great important in the management of diabetic retinopathy. Patients who are in good glucose control at the start of pregnancy and who maintain tight control during pregnancy have little risk of progression of retinopathy. Slowing down the progression of retinopathy and reducing visual loss in pregnancy seems to be possible using laser photocoagulation prior to pregnancy.

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