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# *Review Articles*

# Diabetic Retinopathy in Pregnancy: A Review

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**Abstract**

*Pregnancy in a diabetic woman brings about many changes that can lead to the development of diabetic retinopathy (DR) or worsening of pre-existing disease. In some patients this may develop into sight threatening disease, which if not treated adequately, can cause devastating visual impairment. There is a lack of established guidelines for screening these patients during pregnancy. In this article we discuss the physiological changes during pregnancy that contribute to worsening of diabetic retinopathy and review the relative contribution of risk factors to the underlying pathological processes. It is important to identify and treat any pre-existing retinopathy in diabetic women considering pregnancy and optimise glycaemic control prior to conception. Rapid tightening of glycaemic control after conception is associated with a less favourable outcome. Based on the existing literature we suggest guidelines for diabetic retinopathy screening for women during pregnancy. Established sight-threatening retinopathy should be treated at an earlier stage in pregnant women compared to non-pregnant diabetics with a similar disease.*

***Key words:*** *pregnacy, diabetic retinopathy.*

**Introduction:**

Pregnancy represents a serious challenge to all body systems. The progressive physiological changes that occur are essential to support and protect the developing fetus in addition to prepare the mother for parturition. These physiologic changes involve cardiovascular, renal, pulmonary, hormonal, metabolic, hematologic, immunologic, and visual systems.[1] In the presence of clinical or sub-clinical pathology, the normal physiologic changes of pregnancy can place significant strain on already compromised systems.[1,2]

Ocular complications are common during pregnancy.[3] The number of women with diabetes in pregnancy is increasing, partly as a reflection of increasing obesity in women of child-bearing age.[4] Diabetic retinopathy (DR) is the most common ocular condition modified by pregnancy and pregnancy is associated with an increased risk of development and progression of DR.[4-7] However, there are currently no widely accepted, precise clinical guidelines regarding its management during pregnancy. At present it is not possible to predict who will regress and who will progress without treatment. Some of the variation in progression of DR in pregnancy may be a result of well-known risk factors such as hypertension or inadequate glycemic control prior to pregnancy.[8]

DR developing during pregnancy may show a high-rate of spontaneous regression after delivery. In a study patients with no DR at onset developed mild non-proliferative DR (NPDR) during pregnancy and 50% of them had complete regression, and 30% had partial regression after delivery.[9]

Factors that have been shown to influence the progression of DR in pregnancy include, the pregnant state itself, duration of diabetes, degree of retinopathy at the time of conception, metabolic control of diabetes and the presence of co-existing hypertension .[10] The American Academy of Ophthalmology recommends

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that the pregnant diabetic women should have an ophthalmological examination before conception to determine the baseline severity and then again during the first trimester.[11] Subsequent examination should be every three months until delivery.

**Pathogenesis**

The exact pathogenesis for the progression of DR during pregnancy remains controversial. Some studies demonstrated a decrease in retinal venous diameter and volumetric blood flow in diabetic patients during pregnancy and hypothesized that this may exacerbate retinal ischemia and hypoxia. [12,13] Hormonal changes, changes in the systemic vasculature and retinal auto regulatory mechanisms may be responsible for the worsening of the retinopathy. Hormonal changes in pregnancy include increase plasma levels of human placental lactogen, oestrogen and progesterone hormones. Vascular changes induced by the elevated levels of oestrogen, progesterone and human placental lactogen may contribute to the progression of retinopathy in pregnancy. Of the three hormones, human placental lactogen (hPL) has a very important role in the effect of pregnancy on DR due to its enormous production and growth hormone-like activity. Pregnancy is associated with major changes in the systemic vasculature, which include augmentation in cardiac output and plasma volume and a decrease in the peripheral resistance. [14] This results in a hyperdynamic circulatory state during pregnancy which potentially inflicts additional shear and stress and cause endothelial damage at the capillary level.[15] The auto-regulatory mechanism is impaired in DR due to the loss of capillary pericytes and pregnancy may further worsen it. Thus in a diabetic patient, the physiological changes of pregnancy impose an added stress on an already compromised retinal circulation.

Studies on the influence of pregnancy on the natural history of diabetic retinopathy have shown that deterioration is frequently observed.[16,17] Until recently there has been controversy as to whether the progression of retinopathy, which occurs in such women is due to the natural tendency of diabetic retinopathy to worsen or to unique factors operating during pregnancy. Several major studies have gone some way towards explaining the mechanisms underlying progression of retinopathy during pregnancy. Klein *et al* performed a prospective study on a large series of individuals, comprising 171 pregnant and 298 non-pregnant insulin dependent diabetic women. The level of diabetic retinopathy in the first trimester was assessed using standard retinal photographs and compared with postpartum photographs. After adjusting for duration of diabetes, glycaemic control, and blood pressure, current pregnancy was found to be a major risk factor for the progression of retinopathy.[18] Similarly, Moloney and Drury, also using retinal photography as a means of assessing retinopathy, found that current pregnancy in 53 pregnant diabetic women was associated both with an increased prevalence (from 62% to 77%) and severity of retinopathy whereas in the control group of 39 non-pregnant diabetic women the prevalence of retinopathy remained unchanged at 46% throughout the study period. [16]

Risk factors associated with progression of diabetic retinopathy (DR) during pregnancy

*Duration of diabetes*

Several studies have shown that younger the age of onset and longer the duration of the diabetes higher is the risk of progression of the disease. Progression of diabetic retinopathy was significant in those women with an early onset disease (14±8 years) than in women with a late onset disease (19±8 years). [19] The risk of progression is again high if the duration of the diabetes is more than 15 years. [20] Longer the duration of the diabetes, higher is the chance for the development of microvascular complications, so these patients are likely to have a severe form of baseline retinopathy changes before pregnancy. Hence women with type I diabetes are encouraged to plan pregnancies early in life if possible.

*Severity of retinopathy before pregnancy*

Progression was more significant in women with moderate and severe forms of retinopathy compared to women with mild or no retinopathy at conception.[20] In the diabetes in early pregnancy study (DIEP), 54% women with moderate to severe forms of non-proliferative retinopathy demonstrated disease progression whereas in women with mild retinopathy only 21.1% showed progression.[21] Severe form of retinopathy changes is associated with poor perinatal outcome and in women with severe proliferative changes before conception, pregnancy has to be deferred till the disease is treated or stabilized.

*Metabolic control*

Poor metabolic control is definitely associated with disease progression not only in pregnant diabetic

women but also in non-pregnant diabetic women. Patients with a higher level of glycosylated haemoglobin (7.5%) before conception are more likely to have progression of the disease. Intensive therapy during pregnancy to reduce the foetal and maternal complications has been found to increase the risk of progression of retinopathy. In the DIEP Study,[21] it was clearly shown that those women with the greatest reduction in glycosylated haemoglobin during the first trimester were at an increased risk of progression of DR. DR is a microangiopathy and is associated with narrowing of the smaller caliber vessels. Intensive therapy results in decreased plasma volume which causes closure of the small retinal vessels.[22] In addition, sudden improvement in glycaemia control induces a decrease in the retinal blood flow, with resultant hypoxia and worsening of retinopathy.[23,24] Intensive therapy is associated with a better perinatal outcome; but it may cause worsening of the retinopathy. But it is stated in NICE guideline that Diabetic retinopathy should not be considered a contraindication to rapid optimization of glycaemic control in women who present with a high HbA1c in early pregnancy.[25] So to have a better perinatal outcome without compromising visual loss due to DR, it is better to achieve a gradual good metabolic control before pregnancy rather than a rapid control during pregnancy.

*Hypertension*

Hypertension either pre-existing or pregnancy induced is a known risk factor for progression of retinopathy during pregnancy.[26] Pre-eclampsia was a potent risk factor for the deterioration of retinopathy in type I diabetic patients.[27] Increased systolic and diastolic pressure can affect the retinopathy.[28]

*Effect of diabetic retinopathy on pregnancy*

Several studies have addressed the issue of a possible relationship between the DR and the perinatal outcome. Women with severe form of disease are more likely to develop obstetric complications compared to women with no retinal or minimal retinal changes. [29] Incidence of severe congenital malformations and/or foetal death is higher in patients with proliferative changes.[30] The severity of retinopathy can be correlated with the presence of angiopathy elsewhere, especially the kidneys.[31,32]

*Long term effect of pregnancy on diabetic retinopathy*

Pregnancy does not cause any long term detrimental effects on the retina, kidney and peripheral nervous system.[33,34] Retinopathy changes that have progressed during pregnancy have a tendency to regress after delivery. Even the severe proliferative changes show regression in the postpartum period.As the progression of DR is attributed to the normal hormonal and physiological changes during pregnancy as well as improved glycemic control and hypertensive disorders, these changes regress after pregnancy.

Management of diabetic retinopathy

As DR can progress during pregnancy, diabetic women should have a pre-conception counseling by multidisciplinary team consisting of endocrinologist, ophthalmologist and perinatologist. The patient should be clearly explained about the risk of progression of DR and the importance of good metabolic control before and throughout pregnancy. Close follow-up is needed for patients with longer duration of pregnancy, severe baseline retinopathy, co-existing hypertension and renal disease.

Retinal assessment during pregnancy should be done by digital imaging with mydriasis using tropicamide following the first antenatal clinic appointment and again at 28 weeks if the first assessment is normal. If during the first assessment if there were any DR changes the patient should be seen again around 16-20 weeks. According to NICE guideline, if retinal assessment has not been performed in the preceding 12 months, it should be offered as soon as possible after the first contact in pregnancy in women with pre-existing diabetes. [25]

Women with proliferative changes during pregnancy should have a six months follow-up after delivery. Vaginal delivery is not a contraindication in patients with DR.[36]

A brief summary of recommendations [29] for the management of diabetic patients planning pregnancy or already pregnant is given in Table 1.

In patients with longer duration of diabetes, every effort should be taken to achieve a good metabolic control preferably over a period of weeks or months before conception. If it is not possible, blood sugar levels should be normalized as soon as possible during pregnancy. A glycosylated haemoglobin level of more than six standard deviation above the control mean is associated with progression.[21]

Patients with severe non-proliferative and proliferative changes have a greater tendency for progression

**Table-I**

*Recommendations for management of pregnant patients with type I DM to decrease the risk of progression of DR*

| Time period | Recommendations |
|---|---|
| Pre-conception | • Counsel diabetic women in childbearing years (especially those with pre-existing DR) about the risk of progression<br>• Discuss postponement of conception until ocular disease is treated and stabilized<br>• Diabetic patient should be brought under optimal glycaemic control before conception<br>• Counsel patients about benefits of early pregnancy planning<br>• Comprehensive eye examination to detect pre-existing DR and define the baseline level. |
| First trimester | • Comprehensive eye assessment<br>• Frequent monitoring of blood pressure<br>• Tight glycemic control: First diet control then control of blood sugar |
| Second trimester | • Comprehensive eye examination at the discretion of the examiner, but Preferably every 3 months until delivery<br>• Monitor blood pressure<br>• Tight glycemic control |
| Postpartum | • Conflicting recommendations<br>• Some sources suggest frequent ophthalmologic surveillance for first year |

during pregnancy. So pregnancy should be deferred till the eye disease is treated and stabilized. If progression of the eye disease is noted during pregnancy, prompt laser photocoagulation is indicated in eyes with severe non-proliferative changes and should not be delayed till proliferative changes develop, because proliferative changes tends to progress despite photocoagulation in some eyes. Laser photocoagulation is the mainstay of treatment for DR with reasonable outcomes. [37] Indications for surgery during pregnancy include: tractional retinal detachment, non-clearing vitreous haemorrhage and neovascular glaucoma. Retinal surgery in pregnant women may be difficult, because of the potential problem of pregnant women to lie flat for a considerable period of time. Moreover, presence of neovascular glaucoma with vitreous haemorrhage may be associated with a poor visual outcome.

DR with proliferative changes also shows a strong tendency towards regression after delivery. Patients with severe changes should be closely followed-up in the post-partum period till the diabetic retinal changes stabilize. This includes close retinal surveillance during the first year postpartum.

**Conclusion:**

Pregnancy is a prominent risk factor for the progression of retinopathy. Though development of sight threatening retinopathy is rare during pregnancy, it can have serious consequences for the mother and the foetus. Proper planning of pregnancy in young diabetic women and prompt laser photocoagulation of severe non-proliferative retinopathy can prevent serious sight threatening retinopathy. DR has a definite tendency for regression in the post-natal period and if the retinopathy is stable after delivery there is no risk of progression with subsequent pregnancies.

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