

PERSPECTIVE

Diabetic retinopathy in pregnancy

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Diabetic retinopathy is one of the major causes of preventable blindness in the UK and USA in those aged between 24 and 64 years.¹ For a proportion of diabetic women, the first half of this period coincides with peak fertility and childbearing years. Diabetic eye disease may develop for the first time during pregnancy, and visual loss at this stage has serious implications for both the patient and her family. In the past, the prognosis for pregnancy in diabetic women with microvascular disease was so poor that many physicians advised avoidance or termination of pregnancy.² With the recognition that the level of glycaemia during pregnancy is directly related to the incidence of congenital malformations, the emphasis on the management of diabetic pregnancy has been one of meticulous control of blood sugar and this has undoubtedly resulted in lower rates of fetal malformations. However, intensive control of glycaemia may carry risks to diabetic mothers particularly to those with established microvascular diseases such as retinopathy and nephropathy.

Studies on the influence of pregnancy on the natural history of diabetic retinopathy have shown that deterioration is frequently observed.^{3–4} 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 operative 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.⁵ 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.⁵ 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.³ That retinopathy worsens during pregnancy is now undisputed, although the mechanism by which progression occurs is not entirely clear.

Risk factors for the progression of retinopathy in pregnancy

METABOLIC CONTROL

An elegant study by Phelps *et al*⁶ monitored changes in diabetic retinopathy status during pregnancy and correlated these findings with blood sugar measurements made at corresponding time points. These findings were further supported and extended by the Diabetes in Early Pregnancy Study (DIEP),⁷ a prospective cohort study on

140 pregnant diabetic women who were followed from early pregnancy to delivery using retinal photography. It was clearly shown that those women with the greatest reduction in glycosylated haemoglobin (HbA_{1c}) over the first 14 weeks of pregnancy were at an increased risk of progression of retinopathy.⁷ Patients in whom retinopathy was most likely to progress had both the poorest control at baseline and the largest improvement during early pregnancy. However, it was impossible to separate these two risk factors as virtually all patients had improved metabolic control during early pregnancy.

DURATION OF DIABETES

Another risk factor which has been shown to adversely influence progression of retinopathy is the duration of diabetes before pregnancy.⁸ Dibble *et al* followed 55 insulin dependent diabetic women through their pregnancies and found a positive correlation between duration of diabetes and progression of retinopathy.⁸ However, the results of the more recent and larger DIEP study suggest that duration of diabetes is probably not as important a risk factor for any change in retinopathy as baseline severity of retinopathy. Retinopathy was noticed to progress by two or more steps in 55% of patients with less than 15 years of disease and 50% of those with more than 15 years of disease and these differences were not significant.⁷ But, when the rate of development of retinopathy was compared in patients stratified by duration of diabetes, retinopathy progressed to proliferative levels in 39% of patients with more than 15 years of diabetes as opposed to 18% of patients with a disease duration of less than 15 years.⁷ These findings indicate that duration of diabetes, which is strongly correlated with level of baseline retinopathy, may be a significant factor in the development of more severe change—that is, proliferative retinopathy in pregnancy.

BASELINE SEVERITY OF RETINOPATHY

It has been shown that risk of visual loss is low in those with no pre-existing retinopathy. Approximately 12% of women with no retinopathy at the start of pregnancy will develop minor background retinopathy consisting of a few microaneurysms but regression in the postpartum period is the norm.⁹ Using fluorescein angiography Soubrane *et al* showed that in women with mild background diabetic retinopathy the number of retinal microaneurysms increased progressively during pregnancy but underwent substantial regression postpartum though not quite returning to preconception levels.¹⁰ On the other hand when pre-existing retinopathy is more severe, proliferative changes can develop in a significant number of cases. Thus in the DIEP study, 29% of patients whose fundal appearance was classified as showing moderate retinopathy at baseline went on to develop proliferative changes during pregnancy. This was in contrast with those women who had minimal retinopathy at baseline where only 6.3% progressed to the proliferative category.⁷ These findings

indicate that severity of existing diabetic retinopathy profoundly influences the level of progression.

RETINAL BLOOD FLOW

Pregnancy is associated with major changes in the systemic vasculature. There is an augmentation in cardiac output and plasma volume and a decrease in peripheral resistance, all of which cause increased blood flow. Chen *et al*, using laser Doppler velocimetry to measure retinal blood flow, demonstrated the lack of change of retinal blood flow in normal pregnancy, thus confirming the efficacy of the autoregulatory processes in the retinal vasculature.¹¹ In diabetic patients who showed progression of retinopathy in pregnancy, an increase in blood flow was documented in the first trimester. By contrast, women with diabetes whose retinal blood flow remained unchanged developed no retinopathy.¹¹ They therefore suggested that the hyperdynamic circulatory state of early pregnancy is accompanied by compensatory mechanisms both in normal women and in those diabetes sufferers who retain autoregulatory control of retinal blood flow. In some diabetic women, however, these autoregulatory mechanisms are flawed resulting in an increase in blood flow. Such a hyperdynamic circulatory state could potentially inflict additional shear stress and cause endothelial damage particularly at the capillary level.¹² However, local hypoxia associated with worsening retinopathy could account for the compensatory increase in blood flow which may merely represent an epiphenomenon rather than failure of autoregulation in pregnancy.

HYPERTENSION

Hypertension is a known risk factor for the progression of retinopathy and is additionally hazardous during pregnancy.^{5, 13} Rosenn *et al* followed 154 insulin dependent diabetic women throughout their pregnancies of whom approximately a third had either chronic hypertension or pregnancy induced hypertension or both. Fifty five per cent of those with a hypertensive disorder developed progression of retinopathy as opposed to 25% of those that did not.¹³ Pharmacological treatment of hypertension in pregnancy is most suitable for early onset, severe disease when an attempt to delay delivery is indicated and methyldopa, β blockers, and vasodilators have been used with some success.¹⁴ A recent report has indicated that treatment of women with diabetes with the angiotensin converting enzyme (ACE) inhibitor captopril for 6 months before the onset of pregnancy reduces proteinuria, improves renal function, and is associated with favourable maternal and fetal outcome.¹⁵ In at least one major study all patients with severe proliferative retinopathy also had proteinuria indicating a generalised vasculopathy.⁶ Thus, it is not inconceivable that functional improvement in one circulatory bed might be mirrored in others. However, the use of ACE inhibitors during pregnancy is not recommended as they are extremely fetotoxic resulting in hypotension, renal tubular dysplasia, anuria-oligohydramnios, growth restriction, and death of the fetus.¹⁶ Nevertheless, clinical studies of ACE inhibitors in diabetic retinopathy carried out before the onset of pregnancy might well be worthwhile.

Fundus changes in diabetic retinopathy in pregnancy

Cotton wool spots develop in a proportion of patients with background retinopathy as pregnancy advances and have been seen to be associated with low fasting blood sugar.³ As hypoglycaemia often occurs in the wake of institution of rapid metabolic control,⁶ it has been suggested that low plasma glucose may be responsible for the retinal hypoxia

and damage.³ These morphological alterations are not dissimilar to those observed in non-gravid diabetic individuals who may experience transient worsening of retinopathy when subjected to strict glycaemic control in whom the major changes are cotton wool spots and intraretinal microvascular abnormalities.¹⁷ However, Phelps *et al*⁶ have reported that the components of retinopathy which increased most commonly in pregnancy were haemorrhages and microaneurysms, suggesting that there may be differences in pathophysiological aetiology between gravid and non-gravid subjects.

Effect of diabetic retinopathy on pregnancy

Increasing severity of diabetic retinopathy has been shown to adversely affect outcome in pregnancy. Price *et al* retrospectively reviewed 23 pregnancies in insulin dependent diabetics who had had serial retinal examinations during pregnancy.¹⁸ They noted that 30% of patients who had no observable retinopathy and 70% of patients with background retinopathy at the inception of pregnancy developed obstetric complications. It was noteworthy that all of those with proliferative retinopathy at the start of pregnancy developed pregnancy induced hypertension or other obstetric complications.¹⁸ In another study the impact of diabetic retinopathy on pregnancy was examined in 179 women with diabetes.¹⁹ The pregnancies in 43% of the women with proliferative retinopathy had an unfavourable outcome compared with 13% of those with non-proliferative or no retinopathy and, overall, a fifth of the pregnancies resulted in fetuses with severe congenital malformations and/or fetal death.¹⁹ Thus, severity of retinopathy at baseline was strongly predictive of an adverse outcome in these patients.

Long term consequences of pregnancy on diabetic retinopathy

In an attempt to determine whether pregnancy had an unfavourable effect on retinopathy in the long term Klein and Klein investigated the severity of retinopathy in two groups of diabetic women, one of which had experienced pregnancy and the other had never been pregnant.²⁰ No difference was observed in severity of retinopathy between the groups suggesting the absence of any deleterious effects attributable to pregnancy.²⁰ These findings have been supported by other studies which have shown no long term detrimental effects due to pregnancy in other organs such as the kidney or peripheral nervous system.^{21, 22} Conversely, retinopathy of less overall severity in parous women has been reported,²¹ and the rigorous and intensive control of diabetes instituted during pregnancy in these women has been cited as having a possible protective effect in the long term.

Management of diabetic retinopathy in pregnancy

Before the advent of laser photocoagulation, proliferative retinopathy was a contraindication to pregnancy because of the substantial risk of severe visual loss, so that women with diabetes who became pregnant were advised to consider termination.² With the use of laser photocoagulation and the establishment and recognition of high risk characteristics²³ the likelihood of visual loss has been reduced. Progression of proliferative retinopathy may depend upon whether or not laser photocoagulation has been carried out before pregnancy. One study of patients with proliferative retinopathy detected in early pregnancy and subsequently treated by laser showed that 58% experienced significant progression and visual loss.⁹ On the other hand only 26% of patients in whom retinopathy was diagnosed and treated before onset of pregnancy showed progression of retinopathy during an ensuing gestation

period.⁹ The indications for treatment and the response to laser photocoagulation are exactly the same as for other diabetes sufferers.²⁴ Nevertheless, some studies have found that vascular proliferation is reversible and postpartum regression is common,²⁵ and currently therefore most ophthalmologists would perform a restricted or limited photocoagulation procedure. However, there are a group of women in whom retinopathy is aggressive, responds poorly to photocoagulation, and continues to progress postpartum.²⁶ Thus, it is important that proliferative retinopathy is detected and treated preferably before the onset of pregnancy. Those who develop proliferative retinopathy during pregnancy should have prompt laser photocoagulation treatment sufficient to induce regression.

Sinclair *et al*²⁷ have identified a group of insulin dependent diabetics who developed macular oedema in pregnancy and who also typically developed proteinuria and mild hypertension concomitantly. Laser photocoagulation may be required to treat macular changes but this in itself can exacerbate the oedema particularly in those with a compromised macular capillary circulation. Alternative therapies for this condition include salt restriction diets and diuretics which have been used with limited success.²⁸ When macular oedema occurs it is thought to be due to an ischaemic capillaropathy and may be accompanied by proliferative retinopathy. In some cases macular oedema regresses postpartum but in others it may persist and cause long term visual loss.²⁷ Generally, the diagnosis of sight threatening retinopathy is made on ophthalmoscopic appearances. However, fluorescein angiography is a more sensitive tool to assess the extent of capillary non-perfusion and early neovascularisation and may be of value in the management of pregnant diabetics particularly since there is no evidence that it has any detrimental effect on the developing fetus.²⁹

Despite the tendency for retinopathy to worsen after the institution of strict glycaemic control, there is an overall strong beneficial effect of near normoglycaemia which includes a reduction of retinopathy by 50% at 2 years of follow up.^{30,31} It is also recognised that normalisation of blood sugar during pregnancy is the most important factor for the successful outcome of pregnancy in diabetes,^{32,33} as a high rate of preterm deliveries (39%) and frequent occurrence of intrauterine growth retardation (9%) characterise the fetal outcome in women with uncontrolled diabetes.³⁴ It is therefore recommended that diabetic women who are contemplating pregnancy and who are suboptimally controlled (glycosylated haemoglobin > 6 SD above the control mean) should be targeted for the institution of strict glycaemic control.⁷ Ideally, young women with diabetes should be seen for counselling and management before the onset of pregnancy. Although studies suggest that most patients recognise the value of good blood glucose control,³⁵ a significant proportion may be unaware of the potential risks to vision.

In summary, progression of retinopathy in pregnancy depends on a variety of factors including severity of retinopathy at conception, adequacy of treatment, duration of diabetes, metabolic control before pregnancy, and the presence of additional vascular damage such as pre-existing or concomitant hypertensive disorder. The risks of visual loss in those with minimal retinopathy at the inception of pregnancy are minor, and for these mothers a fundus examination every 3 months should suffice. In those with moderate background retinopathy, funduscopy should be performed at each obstetric visit (which is usually every 4 to 6 weeks) and if progression is detected the patient should be examined at 2 week intervals to detect any high risk characteristics. If high risk characteristics develop photocoagulation should be carried out promptly

and monitored by funduscopy. In those with severe sight threatening retinopathy, laser photocoagulation should be performed before pregnancy or promptly when high risk characteristics develop.

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