# Metabolic Control and Progression of Retinopathy

## The Diabetes in Early Pregnancy Study

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**OBJECTIVE** — To evaluate the role of metabolic control in the progression of diabetic retinopathy during pregnancy.

**RESEARCH DESIGN AND METHODS** — We conducted a prospective cohort study of 155 diabetic women in the Diabetes in Early Pregnancy Study followed from the periconceptional period to 1 month postpartum. Fundus photographs were obtained shortly after conception (95% within 5 weeks of conception) and within 1 month postpartum. Glycosylated hemoglobin was measured weekly during the 1st trimester and monthly thereafter.

**RESULTS** — In the 140 patients who did not have proliferative retinopathy at baseline, progression of retinopathy was seen in 10.3, 21.1, 18.8, and 54.8% of patients with no retinopathy, microaneurysms only, mild nonproliferative retinopathy, and moderate-to-severe nonproliferative retinopathy at baseline, respectively. Proliferative retinopathy developed in 6.3% with mild and 29% with moderate-to-severe baseline retinopathy. Elevated glycosylated hemoglobin at baseline and the magnitude of improvement of glucose control through week 14 were associated with a higher risk of progression of retinopathy (adjusted odds ratio for progression in those with glycohemoglobin $\geq$ 6 SD above the control mean versus those within 2 SD was 2.7; 95% confidence interval was 1.1–7.2; $P = 0.039$).

**CONCLUSIONS** — The risk for progression of diabetic retinopathy was increased by initial glycosylated hemoglobin elevations as low as 6 SD above the control mean. This increased risk may be due to suboptimal control itself or to the rapid improvement in metabolic control that occurred in early pregnancy. Excellent metabolic control before conception may be required to avoid this increase in risk. Those with moderate-to-severe retinopathy at conception need more careful ophthalmic monitoring, particularly if their diabetes was suboptimally controlled at conception.

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DCCT, Diabetes Control and Complications Trial; DIEP, Diabetes in Early Pregnancy Study; hCG, human chorionic gonadotropin; IDDM, insulin-dependent diabetes mellitus.

Metabolic control in early pregnancy has been suggested to be an important risk factor for progression of retinopathy in women with diabetes (1). However, objective retinal evaluation at conception and delivery and concurrent detailed metabolic data have not been available to test this hypothesis. It is important to determine the relationship between metabolic control and progression of retinopathy because pregnancy has been one of the few clinical situations in which aggressive attempts at metabolic normalization have been routinely instituted since even before the release of the Diabetes Control and Complications Trial results (2). Several retrospective (3–5) and prospective studies (6–10) have documented the observation that good glycemic control at conception is associated with reduced rates of spontaneous abortions and infant malformations. In addition, previous studies have also suggested that the physiological changes of pregnancy may influence the rate of progression of diabetic retinopathy (11–17).

The National Institute of Child Health and Human Development's Diabetes in Early Pregnancy Study (DIEP) provided an opportunity to examine progression of retinopathy during pregnancy and associated risk factors for progression. Women with and without diabetes were enrolled in the study before or within 21 days of conception. Stereoscopic fundus photographs were performed at the beginning and the end of the pregnancy only for the women with diabetes. Subjects were monitored extensively throughout pregnancy; thus, it was possible to examine the relationship between glucose control during early pregnancy and progression of diabetic retinopathy.

## RESEARCH DESIGN AND METHODS

— The DIEP was a multicenter collaborative study conducted in clinical centers at Cornell University, Brigham and Women's Hospital (Harvard

**Table 1—*Baseline characteristics of women with and without protocol fundus photographs***

| | With protocol photos | Missing or no photos | *P* value |
|---|---|---|---|
| *n* | 155 | 189 | |
| Race | | | 0.9 |
| White | 147 (94.8) | 179 (94.7) | |
| Black | 5 (3.2) | 5 (2.7) | |
| Other | 3 (1.9) | 5 (2.7) | |
| Education | | | 0.8 |
| High school or below | 31 (20.0) | 33 (17.5) | |
| Some college | 55 (35.5) | 61 (32.3) | |
| College degree | 39 (25.2) | 52 (27.5) | |
| Graduate school | 30 (19.4) | 43 (22.8) | |
| Prior pregnancies | | | 0.96 |
| None | 51 (32.9) | 65 (34.4) | |
| 1 | 50 (32.3) | 60 (31.8) | |
| ≥2 | 54 (34.8) | 64 (33.9) | |
| Prior live births | | | 0.5 |
| None | 50 (48.1) | 59 (47.6) | |
| 1 | 42 (40.4) | 56 (45.2) | |
| ≥2 | 12 (11.5) | 9 (7.3) | |
| Initial glycosylated hemoglobin | | | 0.005 |
| ≤2 SD | 52 (33.5) | 77 (40.7) | |
| >2 SD, ≤4 SD | 41 (26.5) | 57 (30.2) | |
| >4 SD, ≤6 SD | 31 (20.0) | 33 (17.5) | |
| >6 SD, ≤8 SD | 16 (10.3) | 20 (10.6) | |
| >8 | 15 (9.7) | 2 (1.1) | |
| Smoking | | | 0.3 |
| Yes | 28 (18.1) | 26 (13.8) | |
| No | 127 (81.9) | 163 (86.2) | |
| Alcohol consumption | | | 0.5 |
| Yes | 39 (25.2) | 53 (28.0) | |
| No | 116 (74.8) | 136 (72.0) | |
| Age (years) | 27.8 ± 4.1 | 28.1 ± 4.0 | 0.4 |
| Duration of diabetes (years) | 11.9 ± 7.0 | 11.7 ± 6.6 | 0.8 |
| Systolic blood pressure (mmHg) | 110.0 ± 9.6 | 109.1 ± 11.6 | 0.2 |
| Diastolic blood pressure (mmHg) | 69.8 ± 7.5 | 69.5 ± 8.5 | 0.8 |
| Fasting blood glucose (mg/l) | 143.2 ± 57.3 | 144.7 ± 60.9 | 0.8 |

Data are *n* (%) or means ± SD.

University), Northwestern University, the University of Pittsburgh, and the University of Washington. The National Institute of Child Health and Human Development was the data and coordinating center. The primary goals of the DIEP were to assess whether pregnant women with insulin-dependent diabetes mellitus (IDDM) had an increased risk of spontaneous abortion and whether metabolic control affected the rates of malformation in infants of diabetic mothers.

The study design has been described in detail previously (18). Briefly, women with IDDM and nondiabetic control women were enrolled before (86%) or within 21 days of conception (14%). To ensure accurate dating of pregnancy, subjects were encouraged to use basal body temperature monitoring; 57% did so. In all subjects, serum levels of intact or β-human chorionic gonadotropin (β-hCG) were measured 2 days after the expected 1st day of menstruation if menstruation had not begun. If the β-hCG value was equivocal, the test was repeated until a result indicating pregnancy was obtained or vaginal bleeding occurred and a negative result was obtained. Once the diagnosis of pregnancy was established, the women with diabetes were evaluated weekly during the 1st trimester and then monthly for the remainder of the pregnancy. Fundus photographs of seven standard stereo fields were obtained immediately after the diagnosis of pregnancy. Patients were followed until 1 month after the end of the pregnancy, and follow-up fundus photographs were performed either at delivery or within 1 month postpartum.

## Grading of fundus photographs

Fundus photographs were centrally evaluated by the Fundus Reading Center of the University of Wisconsin, using the final scale of the Modified Airlie House Diabetic Retinopathy Classification (19). The protocol for the grading of the photographs was similar to that of the Early Treatment Diabetic Retinopathy Study (19). Each eye was evaluated by a trained grader who had no knowledge of the medical data of the patient, and eyes were categorized into the following clinical groups:

- No retinopathy.
- Microaneurysms or blot hemorrhages only.
- Mild nonproliferative retinopathy: microaneurysms and retinal hemorrhages (less than standard photograph 2A of the Diabetic Retinopathy Study [20]) and the questionable presence of hard exudates, soft exudates, intraretinal microvascular abnormalities, and/or venous beading.
- Moderate nonproliferative retinopathy: microaneurysms and intraretinal hemorrhages greater than or equal to stan-

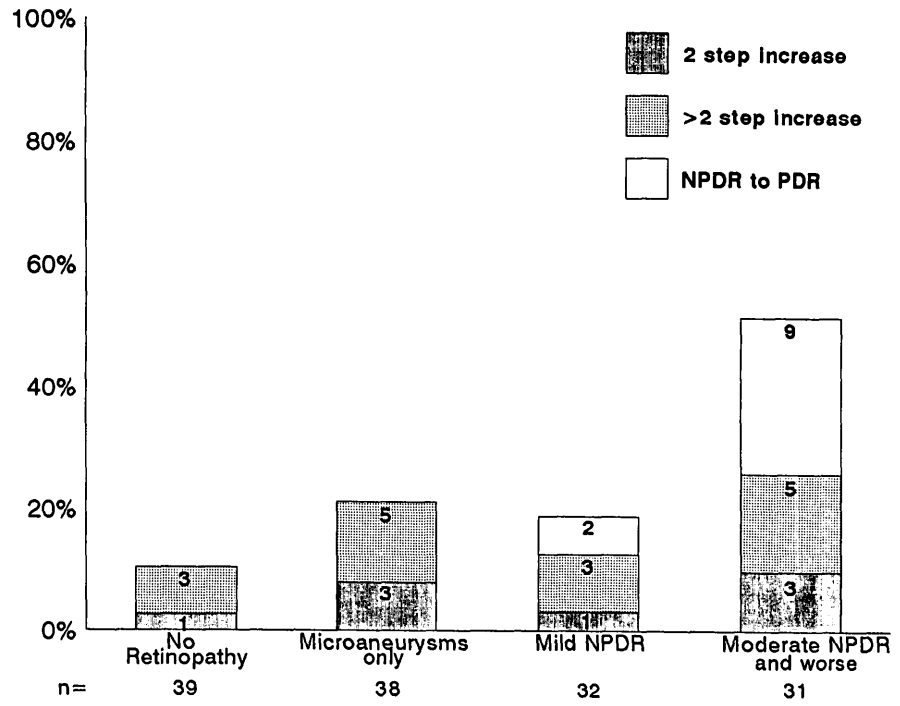


**Figure 1**—*The progression rates of diabetic retinopathy stratified by baseline retinopathy. Patients with more severe diabetic retinopathy were more likely to show progression than those with no retinopathy at baseline ($\chi^2$ for trend, P < 0.001). NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.*

dard photograph 2A in more than three fields, microaneurysms and intraretinal hemorrhages greater than or equal to standard photograph 2A, and the definite presence of hard exudate, soft exudates, intraretinal microvascular abnormalities, and/or venous abnormalities in one field.

- Severe nonproliferative retinopathy: same as moderate nonproliferative retinopathy with lesions found in two or more fields of the standard seven fields of the fundus photographs.
- Proliferative retinopathy: presence of retinal neovascularization.

The photographs from both the baseline and postdelivery visits were independently assessed. Each of the seven standard fields of the fundus photographs was examined for all retinal lesions. A summary measure of all these fields was determined for each eye. For each patient, gradings for both eyes were combined for assessment along this scale. A two-step change along this grading scale was considered to be clinically significant. Progression to proliferative retinopathy was also a clinically important end point. Patients with proliferative retinopathy or evidence of previous scatter photocoagulation for proliferative retinopathy at baseline were not included in the analyses for risk factors for progression of retinopathy.

### Assessment of metabolic control during early pregnancy

Glycosylated hemoglobin was measured using a thiobarbituric acid colorimetric method, which allowed all analyses to be performed in a central laboratory with frozen, washed red cells (21). The results are reported as SD from the mean of the nondiabetic DIEP control population. Glycosylated hemoglobin was assessed weekly during the 1st trimester and monthly thereafter. The initial glycosylated hemoglobin level was determined between 4 and 7 weeks after the last menstrual period in 95% of the subjects.

### Statistical analysis

Comparison of variables expressed as proportions were performed with the $\chi^2$ test. A $\chi^2$ test of trend was also used. Logistic regression analysis was used to evaluate risk factors associated with progression of retinopathy during pregnancy (22).

**RESULTS**— Of the 386 women with diabetes enrolled in the study periconceptionally, 42 had fetal losses. Of the remaining 344 women, 87 did not have any fundus photographs taken, 102 had one of the two required sets of photographs (77 had only baseline photographs and 25 had only postpartum photographs), and 155 had photographs both in early pregnancy and after delivery. Comparison of the socioeconomic and medical characteristics of women who had both fundus photographs with those of women who had either no fundus photographs or only one set of photographs showed that women who had both fundus photographs had higher glycosylated hemoglobin levels at entry ($P = 0.005$) (Table 1). The two groups did not differ significantly in any other risk factor. The baseline level of retinopathy in patients who had only baseline photographs was similar to that in those who had both baseline and follow-up photographs ($P = 0.45$).

### Rates of progression of diabetic retinopathy

The following analysis is based on the 140 women for whom both baseline and postdelivery photographs were available. Fifteen additional patients who had both baseline and postdelivery photographs were excluded from the analysis because they had proliferative retinopathy at baseline or had previously received scatter photocoagulation for proliferative retinopathy. Figure 1 displays the progression rates (≥2-step change) of retinopathy during pregnancy in 140 patients

**Table 2—*Univariate analysis of potential risk factors for progression of diabetic retinopathy***

| | Progression | | Odds | | |
|---|---|---|---|---|---|
| | No | Yes | ratio | (95% confidence interval) | *P* value |
| *n* | 106 | 34 | | | |
| Baseline hemoglobin 6 SD above control mean | 106 | 34 | 2.4 | (1.01–5.91) | 0.048 |
| Baseline retinopathy | | | | | 0.001 |
| No retinopathy (reference) | 35 | 4 | 1.0 | — | |
| Microaneurysms only | 30 | 8 | 2.3 | (0.6–8.5) | |
| Mild NPDR | 26 | 6 | 2.0 | (0.5–7.9) | |
| Moderate NPDR | 15 | 16 | 9.3 | (2.7–32.6) | |
| Gravidity | | | | | 0.18 |
| 0 (reference) | 30 | 15 | 1.0 | — | |
| 1 | 35 | 9 | 0.5 | (0.2–1.3) | |
| 2 | 25 | 3 | 0.2 | (0.1–0.9) | |
| 3 | 11 | 4 | 0.7 | (0.2–2.7) | |
| ≥4 | 5 | 3 | 1.2 | (0.3–5.7) | |
| Smoker | | | | | 0.07 |
| No (reference) | 90 | 24 | 1.0 | — | |
| Yes | 16 | 10 | 2.3 | (0.9–5.8) | |
| Age (5-year increase) | 106 | 34 | 1.0 | (0.7–1.7) | 0.88 |
| Duration of diabetes | | | | — | <0.001 |
| 1–5 years (reference) | 37 | 2 | 1.0 | — | |
| 6–10 years | 25 | 4 | 3.0 | (0.5–17.4) | |
| 11–15 years | 19 | 10 | 9.7 | (1.9–49.0) | |
| 16–20 years | 16 | 13 | 15.0 | (3.0–74.5) | |
| >20 years | 9 | 5 | 10.3 | (1.7–61.8) | |
| Blood pressure (10-mmHg increase) | 106 | 34 | 1.3 | (0.8–2.2) | 0.31 |
| Proteinuria (mg/24 h) | | | | | 0.06 |
| 0–150 (reference) | 87 | 23 | 1.0 | — | |
| 151+ | 11 | 8 | 2.8 | (1.0–7.6) | |

The initial glycosylated hemoglobin level was evaluated as an ordered scale, resulting in a comparison of the value of 6 SD above the control mean with that of the diabetic subjects within the normal range of 2 SD from the control mean. For every 10-mmHg increase in the systolic blood pressure, there was an odds ratio of 1.3 (95% confidence interval 0.8–2.2). NPDR, nonproliferative diabetic retinopathy.

stratified by baseline retinopathy. The risk of progression increased with increasing severity of retinopathy at baseline. A two-step or greater progression or development of proliferative retinopathy was seen in 10.3, 21.1, 18.8, and 54.8% of patients with no retinopathy, microaneurysms only, mild nonproliferative retinopathy, and moderate or more severe nonproliferative retinopathy at baseline, respectively. Patients with no retinopathy or only microaneurysms at conception did not develop proliferative retinopathy. Of those patients with mild and moderate retinopathy at baseline, progression to proliferative diabetic retinopathy was seen in 2 of 32 (6.3%) and 9 of 31 (29%), respectively. Approximately 25% of these patients had high-risk proliferative diabetic retinopathy, as defined by the Diabetic Retinopathy Study (23).

## Risk factors for progression of diabetic retinopathy

The following possible risk factors were examined: initial glycosylated hemoglobin level, gravidity, smoking, age, duration of diabetes, blood pressure, proteinuria, and baseline severity level of diabetic retinopathy (Table 2). Baseline severity of retinopathy ($P = 0.001$), initial glycosylated hemoglobin ($P = 0.048$) (Fig. 2), and duration of diabetes ($P < 0.001$) were significant risk factors in this univariate analysis.

Significant factors from the univariate analyses were then placed in a stepwise multivariable logistic regression model. Increasing severity of baseline retinopathy was associated with increased risk of progression of retinopathy ($P = 0.0001$) (Table 3). Duration of diabetes was highly correlated with increasing severity of baseline retinopathy. Approximately 30% of the DIEP patients had diabetes durations of >15 years. A logistic regression model was performed to assess factors associated with progression of retinopathy and evaluate the relationship between severity of baseline retinopathy

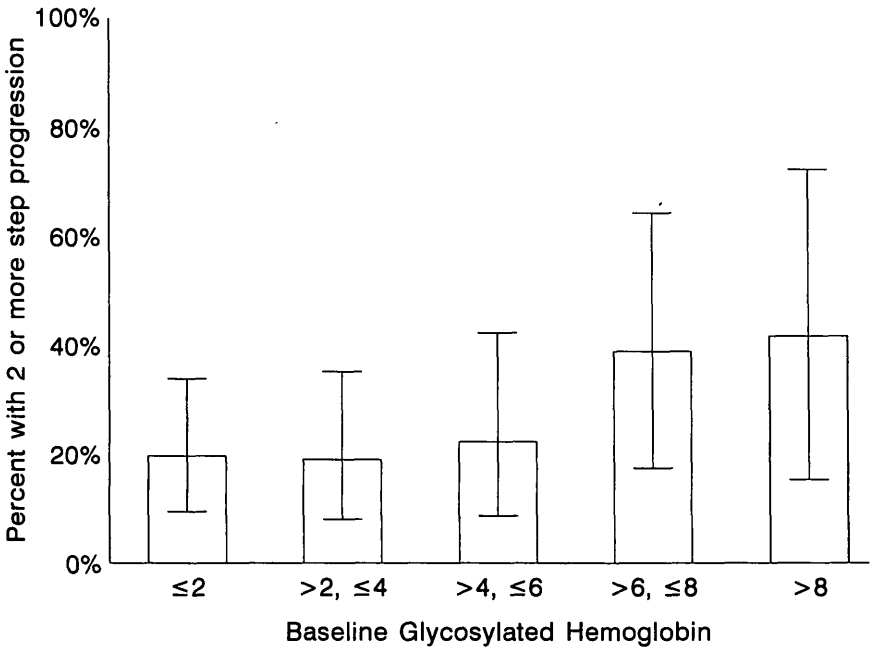


**Figure 2**—*The unadjusted progression rates of diabetic retinopathy (≥2 steps) and 95% confidence intervals by baseline glycosylated hemoglobin values in SD from the control mean. Patients with higher levels of glycosylated hemoglobin were at greater risk of progression ($\chi^2$ test for trend, P = 0.05). The DIEP values expressed in SD correspond to the following values used in the DCCT scale: ≤2 SD: 6.05%; >2, ≤4 SD: 6.05–7.05%; >4, ≤6 SD: 7.05–8.05%; >6, ≤8 SD: 8.05–9.05%; >8 SD: 10.05%.*

and duration of diabetes (<15 years vs. >15 years). Baseline retinopathy was again significant ($P = 0.025$), while duration of diabetes was not ($P = 0.10$). For subsequent determination of logistic regression models, the severity of baseline retinopathy was selected in these analyses. In additional analyses of patients with moderate or more severe retinopathy at baseline in the DIEP, retinopathy progressed by two or more steps (unadjusted) in 55% of patients with ≤15 years of diabetes and 50% of patients with >15 years of diabetes. However, when the rates of development of proliferative retinopathy were compared in patients stratified by duration of diabetes, retinopathy progressed to this stage in 39% of patients with >15 years of diabetes but in only 18% of patients with durations of ≤15 years. Thus, duration of diabetes may not be the most important factor for progression of retinopathy, but it may be significant in the development of proliferative retinopathy.

An elevated glycosylated hemoglobin level at baseline was associated with a higher risk of progression of retinopathy (Fig. 2). Initial glycosylated hemoglobin measurements were evaluated as ordered variables along a scale. For example, women with baseline glycosylated hemoglobin 6 SD above the control mean (8.05% in the DCCT) had an odds ratio of 2.7 (95% confidence interval 1.1–7.2) when compared with women with baseline glycosylated hemoglobin levels within 2 SD of the control mean. Patients in whom retinopathy was most likely to progress had both the poorest control at baseline and the largest improvement during early pregnancy (Fig. 3). It was impossible to separate these two aspects of glucose control with these data because in virtually all patients, poor initial control of diabetes improved during pregnancy.

**CONCLUSIONS** — The DIEP is the first study to include a relatively large number of women with both fundus photographs and detailed metabolic data shortly after conception to assess the effect of metabolic control on retinopathy. The DIEP data showed that the patients in whom retinopathy was most likely to progress had the poorest control of their diabetes at conception. Moreover, in women with less than adequate control of their diabetes, i.e., glycosylated hemoglobin levels >6 SD above the control mean, rates of progression of retinopathy almost doubled, especially if retinopathy was present at conception. Those DIEP patients who had moderate or more severe retinopathy at conception were at significantly greater risk for progression. Patients with no retinopathy or only microaneurysms at conception had a low risk

**Table 3**—***Risk factors for progression of retinopathy in the multivariable logistic regression model***

| | Odds ratio | 95% confidence interval | *P* value |
|---|---|---|---|
| Baseline retinopathy | | | <0.001 |
| Mild NPDR or less | 1.0 | — | |
| Moderate NPDR | 5.7 | 2.1–15.7 | |
| Initial glucose control ≥6 SD above control mean | 2.7 | 1.1–7.2 | 0.039 |

For the multivariable results, variables are considered in stepwise analysis: glucose control, baseline retinopathy, duration of diabetes. The initial glycosylated hemoglobin level was evaluated as an ordered scale, resulting in a comparison of the value of 6 SD above the control mean with that of the diabetic subjects within the normal range of 2 SD from the control mean. NPDR, nonproliferative diabetic retinopathy.

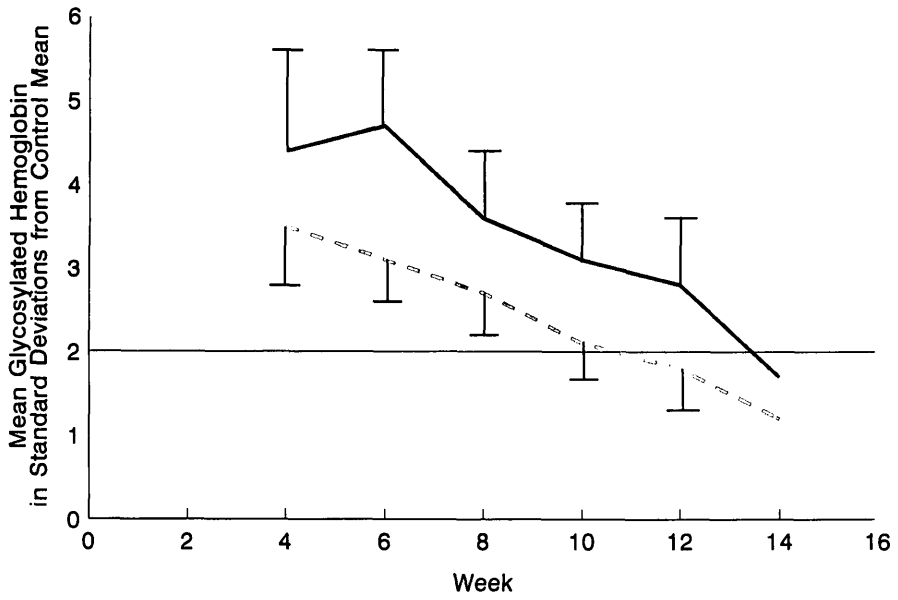


**Figure 3**—*First trimester glycosylated hemoglobin levels with 95% confidence intervals in patients who experienced progression of diabetic retinopathy by ≥2 steps (———) and in patients who did not show progression by ≥2 steps (– – – –).*

for progression, as previously reported by Phelps et al. (1).

The rates of progression of retinopathy in the DIEP were compared with the first annual rates of progression in the Diabetes Control and Complications Trial (DCCT). The DIEP rates of ≥2 steps of worsening in retinopathy were significantly higher than those found in both the experimental treatment (intensive treatment, $P = 0.007$) and the control group of the DCCT ($P < 0.001$). The development of proliferative retinopathy was significantly higher in the DIEP when compared with the DCCT intensive treatment group ($P = 0.04$) and with the conventional treatment group ($P = 0.047$). In some respects, the DCCT population is a suitable group for comparison because the two populations were similar in the severity of retinopathy at baseline and the fundus photographs were graded at the same fundus reading center using the same classifications of retinopathy. The main disadvantage of using the DCCT data for comparison is that the duration of diabetes of DCCT subjects is shorter than that of the DIEP subjects. Limiting the analyses of this study to patients with ≤15 years of diabetes left insufficient power for comparisons with the DCCT subjects.

It is possible that the duration of diabetes may not be as important a risk factor for ≥2-step progression of retinopathy as baseline retinopathy severity is, but duration of diabetes may be a more important risk factor for the development of proliferative retinopathy.

Progression of retinopathy seen in the DIEP may also be explained in part by the improvement of glucose control in early pregnancy. Progression of retinopathy after institution of tight control has been clearly documented in nonpregnant subjects (24–26). The data from the DCCT showed that subjects randomly assigned to the tight metabolic control arm of the study experienced an increased risk of progression of retinopathy within the first 2 years. In the DIEP, the effect of the institution of tight glycemic control is difficult to separate from the effect of elevated glycosylated hemoglobin levels at conception because patients who were most likely to have progression had both the poorest control at baseline and the largest improvement during early pregnancy. These two variables are highly correlated in both this study and clinical practice. A further confounding factor is the correlation of increasing severity of retinopathy with increasing poor glucose control at baseline.

The DIEP results have important clinical implications. Women with moderate or more severe retinopathy at conception are at a greater risk of progression of retinopathy during pregnancy. Patients with significant retinopathy who have suboptimal metabolic control at conception are at greatest risk for progression. Proliferative diabetic retinopathy may develop, and careful ophthalmic monitoring is indicated. The routine practice of instituting tight glycemic control in early pregnancy may also contribute to worsening retinopathy. However, numerous studies indicate that good diabetic control around the time of conception and throughout organogenesis reduces the risks of spontaneous abortion and malformation (13–17). Furthermore, the long-term beneficial effects of sustained tight glucose control include a reduction of retinopathy by as much as 50–70% at 7 years of follow-up (2). We suggest that women with diabetes who are contemplating pregnancy but have less than adequate control of their diabetes (i.e., glycosylated hemoglobin >6 SD above the control mean) should be brought into tight glycemic control before conception, especially if retinopathy is present. Improving metabolic control before pregnancy to prevent progression of retinopathy offers the best opportunity for a favorable outcome for the mother and the infant.

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