Retinal Blood Flow Changes During Pregnancy in Women With Diabetes

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Purpose. To study retinal blood flow (RBF) during pregnancy in subjects with and without diabetes and to relate the changes to progression in diabetic retinopathy.

Methods. RBF in a major temporal retinal vein was measured, where possible, during all three trimesters (T1 to T3) and the postpartum period (PP) using laser Doppler velocimetry (measuring velocity [V]) and monochromatic fundus photographs (measuring diameter [D]).

Results. In the subjects without diabetes (n = 19), no significant change in RBF was demonstrated. V was significantly greater in T3 than in PP (P = 0.01). D was significantly smaller in T1 to T3 than in PP (P < 0.01). RBF in the subjects with diabetes was significantly higher in T2 and T3 than in PP (P < 0.05). V increased from T1 to T2 (P = 0.04) and decreased from T2 to PP (P = 0.001) and from T3 to PP (P = 0.002). The only significant change in D was a smaller value in T1 than in PP (P = 0.003). However, it was only those subjects whose DR progressed (n = 11) who had a significant increase in RBF during pregnancy (P = 0.0001).

Conclusions. These data suggest that the hyperdynamic circulation present in pregnancy led to compensatory retinal vessel constriction (autoregulation) in the group without diabetes; this was largely absent in the patients with diabetes, with resultant increase in retinal blood flow associated with worsening retinopathy. This finding lends further support to the hypothesis that increased retinal blood flow is a pathogenic mechanism for diabetic retinopathy. Invest Ophthalmol Vis Sci. 1994;35:3199-3208.

There is considerable evidence indicating that diabetic retinopathy (DR) is adversely affected by pregnancy.1-8 Women with preexisting DR, especially those with moderate to severe disease, are at risk of progression to a sight-threatening stage. Although many undergo some degree of resolution in the postpartum period, others are in urgent need of treatment during pregnancy.

Klein et al, comparing the rate of progression of DR between a group of pregnant women with diabetes and a group of nonpregnant women with diabetes, found that the pregnant women had a significantly higher rate of progression after accounting for the influence of glycemia control and blood pressure.1 Similarly, Moloney et al discovered that pregnancy increased both the incidence of DR and its rate of progression.2

The pathogenesis of DR is unclear, but it includes hemodynamic, rheologic, and biochemical factors. Abnormalities of retinal blood flow and its regulation in patients with diabetes mellitus have been shown by many investigators.9-17 It has been proposed that increased retinal blood flow leading to increased shear stress on the vascular endothelium is an important pathogenic mechanism for DR.12

Pregnancy is a period of immense physiological change. On average, there is a 40% increase in cardiac output resulting from increases in heart rate, cardiac contractility, and circulating volume, combined with decreased peripheral vascular resistance.18 This may lead to increased retinal blood flow, which in a diabetic eye, with its compromised regulatory mechanism, may be one reason retinopathy worsens during pregnancy. The aim of the present study was, therefore, to investigate retinal blood flow changes during pregnancy in a group of healthy pregnant women in comparison with
a group of pregnant women with diabetes, and to relate these to changes in DR.

METHODS

Twenty-two subjects with diabetes and 19 subjects without diabetes were studied. Table 1 shows their clinical characteristics. Informed consent was obtained from all subjects, and the research protocol was in accordance with the tenets of the Declaration of Helsinki and was approved by the Hammersmith Hospital Research Ethical Committee.

Each subject was studied, if possible, once during each trimester (T1 to T3) and once during the postpartum period (PP), for a maximum of four visits. At each visit, retinal blood flow was assessed with bidirectional laser Doppler velocimetry (BLDV) and monochromatic fundus photography (see below for details). The patients with diabetes had standard seven-field fundus photographs taken, and their retinopathy status was graded using the ETDRS classification.\textsuperscript{19} Brachial arterial blood pressure and intraocular pressure were measured. Diabetic control was determined from glycated hemoglobin levels (HbA\textsubscript{1c}).

Not all patients were studied at all four times; it was especially difficult to see patients during the first trimester, and a few patients missed a mid-pregnancy visit. As a result, direct comparison among the four study periods was not possible because each period included at least one patient for whom there was no data in one of the other three. When comparing each period with any other, data analysis was limited to those patients who attended both periods being compared; patients in either period who did not attend the other were excluded from that comparison. It was possible to follow seven patients with diabetes and two control patients all the way through from the first trimester.

Because no prepregnancy baseline data were available, the postpartum data were considered to be baseline. On average, this was 20.5 weeks after giving birth for the group with diabetes and 18.1 weeks after giving birth for the control group. Hemodynamic changes have been shown to be at the prepregnancy levels by 6 to 8 weeks postpartum.\textsuperscript{20}

### TABLE 1. Patient Characteristics at Entry Into the Study

<table>
<thead>
<tr>
<th></th>
<th>With Diabetes</th>
<th>Without Diabetes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>29.3 ± 5.3 years</td>
<td>30.9 ± 4.4 years</td>
<td>0.5</td>
</tr>
<tr>
<td>Duration</td>
<td>12.9 ± 9.0 years</td>
<td>NA</td>
<td>0.6</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>109.2 ± 15.0 mm Hg</td>
<td>106.0 ± 10.6 mm Hg</td>
<td>1.0</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>66.5 ± 8.9 mm Hg</td>
<td>65.6 ± 6.9 mm Hg</td>
<td>NA</td>
</tr>
</tbody>
</table>

NA = Not applicable.

#### Bidirectional Laser Doppler Velocimetry

Retinal blood velocity was measured with the BLDV, which delivers a low-power helium–neon laser (wavelength 632.8 nm) beam into the eye focused upon the vessel of interest.\textsuperscript{21} The moving erythrocytes in the vessel cause a shift in the frequency of the reflected laser beam, which is collected bidirectionally by two photodetectors. Each photodetector produces a photocurrent that is analyzed by a signal analyzer and fed into a Masscomp 5500 super minicomputer. A computer algorithm determines the maximum frequency shift and calculates the maximum center-line erythrocyte flow rate ($V_{\text{max}}$); the mean velocity ($V_{\text{mean}}$) is calculated by dividing $V_{\text{max}}$ by a factor of 1.6.\textsuperscript{22}

Measurements were made in a superior or inferior temporal retinal vein within 1 disc diameter of the optic disc margin; venous flow was studied because of its minimal pulsatility, which improves the accuracy of the measurement. It has previously been shown that blood flow is similar in the superior and inferior temporal veins and also that venous flow is similar to its corresponding arterial flow, with a vein draining over 95% of its accompanying artery.\textsuperscript{23,24} A Polaroid (Hertfordshire, UK) photograph was taken at the first visit to mark the site of the BLDV measurement; this provided reference for subsequent visits as well as for vessel diameter measurements.

#### Monochromatic Fundus Photographs

Three fundus photographs were taken with each BLDV measurement using a standard Zeiss 30° fundus camera (Carl Zeiss, Oberkøchen, Germany). The camera shutter was synchronized with an ECG monitor, to which the subjects were connected, to minimize variability induced by the cardiac cycle.\textsuperscript{25} High-contrast Technical Pan film (Eastman Kodak, Rochester, NY) was used. The camera was fitted with a 570 nm filter to obtain monochromatic, red-free photographs, which increases the resolution of the blood vessels.\textsuperscript{26}

The photographs were analyzed using the Context Vision Digital Image Analysis system (Context Vision, Linköping, Sweden).\textsuperscript{27} A high-resolution television camera scans the negatives, and the image is digitized to a 512 X 512 array by the Image Analysis computer. The site of BLDV measurement is indicated by a cur-
sor that cuts across the vessel perpendicularly. The computer generates a transmittance profile of this site. Background and peak intensity values of this profile are marked, and from this the computer determines the half-height; the width across the profile at its half-height is taken as the vessel diameter. Three measurements were made of each of the three photographs to give the average diameter.

**Blood Flow Calculations**

Volumetric blood flow was calculated using the following formula:

\[ Q = V_{\text{mean}} \cdot \pi \cdot D^2 / 4 \]

\( Q \) = blood flow, \( V_{\text{mean}} \) = mean red cell velocity, \( D \) = vessel diameter

The ocular perfusion pressure is calculated as shown in the following formula:

\[ PP = 2/3 \text{MAP} - \text{IOP} \]

\( PP \) = perfusion pressure, \( \text{MAP} \) = mean brachial arterial blood pressure, \( \text{IOP} \) = intraocular pressure

**Statistical Analysis**

The distribution of results was assessed for normality using the Shapiro Francia W test. If the data were found to exhibit normal distribution, paired and unpaired Student's t-tests were used for assessing intra-group and intergroup differences, respectively. If the data did not exhibit normal distribution, the Wilcoxon matched pairs signed rank sum test was used. Comparisons were made between the three trimesters and between each trimester and the postpartum period. Regression analysis was used to assess the relationship between changes in perfusion pressure and blood flow parameters. Data are presented as mean ± standard error, or median and 25% and 75% percentile, as appropriate. A probability of 0.05 was considered to be statistically significant.

**RESULTS**

**Clinical Characteristics**

There was no significant difference in age or blood pressure levels between the group with diabetes and the group without it at entry into the study \( (P > 0.05) \) (Table 1).

**Diabetic Retinopathy Status**

At entry into the study, of the 22 patients with diabetes, six had no DR, 12 had background DR (BDR), two had early proliferative DR (PDR) with new vessels elsewhere, one was receiving panretinal photocoagulation treatment for proliferative disease, and one had previous laser treatment for PDR (Table 2).

In five of the six patients without DR, mild BDR developed; one patient, though, regressed to no DR status after giving birth. In four patients, BDR progressed either to a more severe level of BDR (two patients) or to PDR (two patients). Of the two with PDR at entry, one progressed and the other regressed spontaneously to BDR. The status of the patient who was receiving laser treatment at entry deteriorated further during pregnancy, whereas the status of the patient who had full panretinal photocoagulation remained stable.

**Retinal Blood Flow Parameters**

**Blood Pressure.** There was no significant difference in the mean arterial pressure (MAP) between the group with diabetes and the control group at entry into the study \( (P > 0.5) \). Table 3 summarizes the following hemodynamic parameters.

The group with diabetes had significantly lower diastolic blood pressure in T1 and T2 than in PP \( (P < 0.05) \). In this group, both systolic and diastolic pressures rose from T2 to T3 \( (P < 0.05) \). These changes are reflected in the MAP, which was also significantly different between these periods \( (P < 0.05) \). The perfusion pressure also changed significantly between these periods.

**TABLE 2. Diabetic Retinopathy Changes During Pregnancy**

<table>
<thead>
<tr>
<th>DR Status at Entry</th>
<th>Change in DR Status During Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DR (N = 6)</td>
<td>Mild BDR developed in five (ETDRS 20–30); one reverted to no DR (ETDRS 10) postpartum.</td>
</tr>
<tr>
<td>BDR (N = 12)</td>
<td>Four experienced worsening of their DR status: two to PDR (ETDRS 41 to 61; 45 to 65) and two to a more severe level of BDR (ETDRS 30 to 41). Of the two with PDR, one reverted spontaneously postpartum and one after treatment for NVE during pregnancy.</td>
</tr>
<tr>
<td>PDR (N = 2)</td>
<td>One experienced a slight progression (ETDRS 61 to 65), whereas the other reverted spontaneously to BDR level (ETDRS 65 to 41).</td>
</tr>
<tr>
<td>Treated (N = 2)</td>
<td>One had quiescent DR that did not alter during pregnancy, whereas the other was still receiving laser treatment, in spite of which there was further deterioration (ETDRS 61 to 65).</td>
</tr>
</tbody>
</table>

ETDRS classification: 10 = no DR; 20–55 = BDR; >61 = PDR. DR = Diabetic retinopathy; BDR = background diabetic retinopathy; PDR = proliferative diabetic retinopathy; NVE = new vessels elsewhere.
sion pressure was significantly lower in T1 than in PP and in T2 than in T3 (P < 0.05).

In the control group, diastolic pressure was lower in T2 than in PP (P = 0.02). No significant changes were detected in either the systolic or the mean arterial pressure. The perfusion pressure, however, increased significantly between T1 and T3 (P = 0.05). Therefore, blood pressure tended to be lower in early pregnancy than in late pregnancy and the postpartum period; this observation was true for both groups.

Retinal Blood Velocity. Retinal blood velocity increased as pregnancy progressed, particularly in the subjects with diabetes, with a reduction in the postpartum period.

In the subjects with diabetes, V_max was significantly higher in both T2 and T3 than in T1 by 22.3 ± 9% (P = 0.004) and 34.4 ± 12% (P = 0.02), respectively. There was no difference in V_max between T1 and PP, but it was higher in both T2 and T3 than in PP by 20.7 ± 5% (P < 0.001) and 22.8 ± 5% (P = 0.001), respectively (Table 4).

In the control group, V_max was significantly higher in T3 than in PP (P < 0.01) (Table 4).

Vessel Diameter. There was no significant change in vessel diameter in the group with diabetes except that in T1, the vessel diameter was narrower than in PP by 10.9 ± 3% (P = 0.005) (Table 5). There was a trend for an increase in the diameter from T1 to the later two trimesters, but these changes did not reach statistical significance. The diameters at T2 and T3 were not significantly different from the postpartum value (P > 0.05).

| TABLE 3. Changes in BP Through Pregnancy to Postpartum |
|-----------------------------------|----------------|----------------|----------------|----------------|
| **With Diabetes** | **T1** | **T2** | **T3** | **PP** |
| MAP | 54.8 (1.2)* | 53.4 (1.4)* | 58.6 (2.0)† | 58.1 (1.1) |
| BPs | 109.5 (2.5) | 111.2 (3.5) | 119.5 (5.0)† | 114.6 (3.7) |
| BPD | 68.5 (1.0)* | 65.6 (1.8)* | 72.5 (2.7)† | 73.7 (1.0) |
| Perf pres | 39.3 (1.3)* | 38.1 (1.6) | 43.8 (2.2)† | 42.5 (1.2) |

<table>
<thead>
<tr>
<th><strong>Without Diabetes</strong></th>
<th><strong>T1</strong></th>
<th><strong>T2</strong></th>
<th><strong>T3</strong></th>
<th><strong>PP</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP</td>
<td>55.7 (1.9)</td>
<td>52.5 (1.3)</td>
<td>54.6 (1.4)</td>
<td>53.1 (1.4)</td>
</tr>
<tr>
<td>BPs</td>
<td>109.3 (1.9)</td>
<td>106.7 (3.4)</td>
<td>106.9 (2.6)</td>
<td>105.1 (2.4)</td>
</tr>
<tr>
<td>BPD</td>
<td>69.7 (4.1)</td>
<td>63.5 (1.8)*</td>
<td>68.6 (2.0)</td>
<td>68.6 (2.0)</td>
</tr>
<tr>
<td>Perf pres</td>
<td>38.7 (3.4)</td>
<td>36.7 (1.3)</td>
<td>39.7 (1.9)*</td>
<td>37.8 (1.6)</td>
</tr>
</tbody>
</table>

The above figures represent means for all the patients in any given study period. When comparing one period with another, the figures used for any particular comparison vary slightly because the number of patients studied varied between the different periods; patients not common to both periods compared were excluded from that particular comparison. Data are presented as mean (SEM) in mm Hg. MAP = Mean arterial blood pressure; BPs = systolic blood pressure; BPD = diastolic blood pressure; Perf pres = perfusion pressure.

* Significantly less than PP (P < 0.05); †significantly greater than T2 (P < 0.05); ‡significantly greater than T1 (P = 0.05).

| TABLE 4. Retinal Blood Velocity Changes |
|----------------------------------------|----------------|----------------|----------------|
| **With Diabetes** | **Percentage Change** | **Significance** | **N** |
| T1 | 5.4% (8.6) | 1.9 (0.2) to 1.8 (0.1) | cm/sec | P = 0.2 | 9 |
| T2 | 20.7% (4.5) | 2.2 (0.2) to 1.7 (0.1) | cm/sec | P = 0.0003 | 14 |
| T3 | 22.8% (4.9) | 2.2 (0.1) to 1.7 (0.1) | cm/sec | P = 0.001 | 15 |

| **Without Diabetes** | **Percentage Change** | **Significance** | **N** |
| T1 | 92.4% (34.1) | 2.4 (0.2) to 1.5 (0.2) | cm/sec | P = 0.08 | 12 |
| T2 | 14.2% (7.0) | 2.2 (0.1) to 1.9 (0.2) | cm/sec | P = 0.004 | 16 |
| T3 | 17.8% (5.2) | 2.3 (0.1) to 1.8 (0.1) | cm/sec | \( \times \) |

T1 = first trimester, T2 = second trimester, T3 = third trimester. This table compares each trimester of pregnancy with the postpartum value, which was used as the baseline value. The actual values are presented below the percentage change, in parentheses, with the value for the period in question first, followed by the postpartum value. The postpartum values are different in each of the three comparisons because the number of patients in the study increased toward the latter part of pregnancy. When comparing T1 with postpartum, only the values for those patients common to both these periods have been used; because T2 and T3 will have more patients than T1, their corresponding postpartum values will be different from those in the T1 comparison and with each other. Results are presented as mean (SEM).
The control subjects had smaller vessel diameters in each trimester than in PP. The respective changes from T1, T2, and T3 to PP were 11.2 ± 1% (P = 0.01), 6.2 ± 2% (P = 0.005), and 7.4 ± 2% (P = 0.01) (Table 5).

Volumetric Flow. The subjects with diabetes exhibited significantly higher volumetric blood flow rates in T2 and T3, compared with PP, of 14.2 ± 10% (P = 0.04) and 19.3 ± 8% (P = 0.02), respectively (Table 6). Flow in T1 was similar to that in PP, and there was a trend for an increase from T1 to the later two trimesters, but the increases did not reach statistical significance.

The control subjects showed no significant change in volumetric flow between any of the three trimesters or when compared with PP. There was a trend for higher flow rates during pregnancy, but this did not reach statistical significance (P > 0.09) (Table 6).

There was no correlation in either group between flow and perfusion pressure changes. Although the percentage change between each trimester and PP was consistently larger in the group with diabetes when compared with the control group, the difference between them was not statistically significant (P > 0.05); this was also true for V_max, and the converse was true for vessel diameter. This failure to find a difference between them is probably due to a combination of the relatively small number of comparisons possible and the large variation in the results within each group.

Figures 1 and 2 present the retinal blood flow for all patients in each trimester through postpartum.

Relation of Blood Flow to Diabetic Retinopathy. Blood flow parameters behaved differently in those patients with diabetes whose retinopathy deteriorated compared to those in whom it remained stable. Those in whom it deteriorated had significantly greater retinal blood velocities in all three trimesters than in PP (P ≤ 0.05). Those in whom it did not show similar but...
smaller changes, with only the values of the later two trimesters significantly greater than PP ($P < 0.05$).

Those in whom it deteriorated showed no significant change in vessel diameter when comparing T1, T2, and T3 with PP. In the stable group, however, the diameter measurement was significantly smaller in T1 than in PP ($P < 0.05$), although in the later two trimesters there was no significant difference from PP.

The group whose retinopathy worsened had significantly higher volumetric flow in T1 and T3 than in PP ($P < 0.05$). Although the flow in T2 was also higher than PP, this missed statistical significance ($P = 0.06$). In contrast, the stable group exhibited no difference in flow between any of the trimesters and the postpartum period.

In summary, volumetric flow in the group with diabetes increased significantly during pregnancy only in those whose retinopathy status worsened (Table 7). There was no significant difference in age, duration of diabetes, or blood pressure changes between those who deteriorated and those who remained stable.

Glycemia Control

The mean HbA$_1c$ values improved significantly in the group with diabetes as pregnancy progressed ($P < 0.05$). HbA$_1c$ data in early pregnancy (less than 8 weeks gestation) were available for 8 of the 11 patients whose DR progressed and for 6 of the 11 in whom it did not (Table 8). Those who progressed had a mean value of 8.7% ± 0.8% in early pregnancy that improved to 6.0% ± 0.5% ($P < 0.05$), whereas those who remained stable improved from 7.6% ± 0.6% to 5.2% ± 0.3% ($P < 0.05$). The mean improvement in HbA$_1c$ values was 2.7% ± 0.6% and 2.5% ± 0.7% for the progressed and stable groups, respectively; there was no difference in the degree of improvement achieved between the two groups ($P > 0.05$). Although the group who progressed had a higher HbA$_1c$ value initially, the difference was not significant ($P > 0.05$).

The four patients who suffered the worst progression had poorer glycemia control in early pregnancy, with a mean HbA$_1c$ of 9.9% ± 1.3%. They also underwent a greater degree of improvement in control, achieving an HbA$_1c$ value of 6.4% ± 0.7% by late pregnancy.

DISCUSSION

Many studies have shown that the incidence and progression of DR are increased by pregnancy. This study showed increased retinal blood flow during pregnancy in patients with diabetes by 14% to 19%, but only in those whose retinopathy progressed. The increase in blood flow was principally due to increased velocity.

The subjects without diabetes showed no significant changes in flow. Although there was an increase in velocity, their vessel diameters were 6% to 11% smaller in all three trimesters compared with the postpartum value. This last point contrasted with the subjects with diabetes. It can be inferred that the control subjects exhibited a reduction in vessel diameter in response to increased blood flow reaching the retina, as evidenced by the increased velocity, thus preventing the increase from being transmitted into the retinal vessels and keeping retinal blood flow constant. This is in accordance with the definition of autoregulation in its strictest sense, which states that autoregulation is the intrinsic tendency of an organ to maintain a constant blood flow in the face of changing perfusion pressure.

In subjects with diabetes, the only significant change in vessel diameter was a small reduction during the first trimester, significant only in those whose retinopathy did not progress. This suggests a failure of autoregulation in the patients whose retinopathy deteriorated and a limited response in those whose retinopathy remained unchanged. This finding is in agreement with many other studies that have shown a failure of autoregulation in patients with diabetes.
TABLE 7. Relation of Retinal Blood Flow Parameters to Changes in Diabetic Retinopathy

<table>
<thead>
<tr>
<th></th>
<th>Velocity</th>
<th>Diameter</th>
<th>Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Progressed</td>
<td>Stable</td>
<td>Progressed</td>
</tr>
<tr>
<td>T1</td>
<td>18.3 ± 3.2*</td>
<td>-1.0 ± 12.3</td>
<td>-1.2 ± 1.7</td>
</tr>
<tr>
<td></td>
<td>N = 3</td>
<td>N = 6</td>
<td>N = 3</td>
</tr>
<tr>
<td>T2</td>
<td>24.5 ± 6.1*</td>
<td>18.6 ± 6.2*</td>
<td>-2.3 ± 1.9</td>
</tr>
<tr>
<td></td>
<td>N = 5</td>
<td>N = 9</td>
<td>N = 5</td>
</tr>
<tr>
<td>T3</td>
<td>32.4 ± 6.6*</td>
<td>14.3 ± 5.8†</td>
<td>2.1 ± 1.5</td>
</tr>
<tr>
<td></td>
<td>N = 7</td>
<td>N = 8</td>
<td>N = 7</td>
</tr>
</tbody>
</table>

This table shows the percentage difference in retinal blood velocity, vessel diameter, and volumetric blood flow between each of the trimesters (T1 to T3) and the postpartum period comparing those whose diabetic retinopathy progressed during pregnancy and those in whom it remained stable. A negative sign indicates a lower value during pregnancy compared to the postpartum period. Values are presented as mean ± SEM.

* P < 0.01; † P < 0.05; ‡ P = 0.06.

The site of autoregulation in the retinal circulation is uncertain, probably in the resistance vessels. The vessel measured in this study was a vein, unlikely to play an active role, but, because it drains more than 95% of its accompanying artery, it mirrors any active autoregulatory changes exhibited by the artery.

Although the perfusion pressure during pregnancy was not significantly different from what it was during the postpartum period in either group, the increased flow could have resulted from the reduced peripheral vascular resistance that may have involved the retinal vasculature. Blood pressure is normally reduced during pregnancy as shown in this and another study. In spite of this, blood flow has similarly been demonstrated to be increased in many organs, for example, the cerebral cortex, skin, and kidneys. Our results are broadly in agreement with the findings of Ogasawara et al, although they found larger increases in flow; theirs was a smaller study comprised of only six patients who had their blood flow measured twice.

Increased retinal blood flow in patients with diabetes has previously been demonstrated using different investigative techniques, and it has also been found that retinal blood flow increases with increasing severity of DR and decreases after panretinal photocoagulation. The pathogenesis of DR is likely to be multifactorial, with chronic and fluctuating hyperglycemia the common denominator. Hyperglycemia has been shown by many investigators to increase retinal blood flow significantly. Keen et al showed an increase in retinal lactate levels under conditions of hyperglycemia in vitro; this could mimic a hypoxic environment leading to compensatory hyperperfusion. It has also been proposed that hyperglycemia induces the release of nitrous oxide by endothelial cells, a potent vasodilator.

Increased blood flow can result from several other factors known to exist in diabetes. Pericytes, which are lost early in the disease process, have been shown to possess contractile properties and are, therefore, likely to be important in the regulation of blood flow.

TABLE 8. Glycemic Control Changes

<table>
<thead>
<tr>
<th></th>
<th>Early Pregnancy</th>
<th>Late Pregnancy</th>
<th>Level of Changes</th>
<th>Significance</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>P</td>
<td>8.7% (0.8)</td>
<td>6.0% (0.5)</td>
<td>2.7% (0.6)</td>
<td>P &lt; 0.05</td>
<td>8</td>
</tr>
<tr>
<td>NP</td>
<td>7.6% (0.6)</td>
<td>5.2% (0.3)</td>
<td>2.5% (0.7)</td>
<td>P &lt; 0.05</td>
<td>6</td>
</tr>
<tr>
<td>WP</td>
<td>9.9% (1.3)</td>
<td>6.4% (0.7)</td>
<td>3.5% (1.0)</td>
<td></td>
<td>4</td>
</tr>
</tbody>
</table>

This table presents the mean HbA1c values for the patients with diabetes, separated into those whose diabetic retinopathy status progressed and those in whom it remained stable. The four patients who experienced the greatest progression are shown separately, although their values were included in the total group of eight whose retinopathy progressed. Early pregnancy means before the eighth week of gestation, and the late pregnancy value was derived from the best control achieved in the second or third trimester. Because early pregnancy data were not available for all patients, the number of patients presented here is less than the total number of patients with diabetes studied.

P = Retinopathy progressed; NP = retinopathy did not progress; WP = worst progression in retinopathy.
pericytes. This response of the pericytes to endothelin has been shown to be blunted in the presence of high glucose. Capillary occlusion, another feature of DR, leads to retinal ischemia that may result in compensatory hyperperfusion in the surrounding vessels. Hence, there are many reasons for the increase in retinal blood flow in diabetes. Increased blood flow in diabetes mellitus is not unique to the retina; it has been found in the kidney and peripheral tissues as well.

This study has demonstrated an association between progression of retinopathy with increased retinal blood flow; however, association does not necessarily indicate cause. It has been postulated by several investigators that there is indeed a causative link. The increase in flow, by generating increased shear stress, may inflict injury upon the endothelial cells of the retinal vessels, particularly at the capillary level. Wolbarsht et al proposed that vessel dilatation from increased flow leads to vascular stretching and, subsequently, to a breakdown of the blood-retinal barrier. This has been postulated as being a mechanism through which microaneurysms, an early feature of DR, may develop; this is made more likely by the early loss of pericytes in the disease process. It has, however, been shown that vessels are normally able to dilate in response to increased flow; this may be a protective response to reduce the degree of shear force on the endothelium. In the diabetic circulation, this protective mechanism may be limited by the presence of a thickened basement membrane, an early feature of DR, which limits dilatation and thereby accentuates any shear stress damage consequent upon increased flow. Increased flow may itself lead to a thickened basement membrane.

This sequence of events may initiate or compound any previous anatomic damage induced by the abnormal biochemical environment of diabetes and allow a self-perpetuating cycle of damage to prevail. It is, however, possible that increased blood flow may be just an associative phenomenon of worsening retinopathy because of the increasing degree of hypoxia; to address this question fully, a prospective investigation would have to be performed on a group of patients without retinopathy who are followed up with regular blood flow assessments and fluorescein angiography until DR develops.

Other ocular diseases in which there is likely to be increased blood flow have been found to produce signs similar to those of DR. Among these are retinal angiomatosis and Coats' disease; both conditions are associated with arteriovenous shunt formation and, thus, with increased blood flow. The retinal features common to these conditions are among those seen in diabetic retinopathy, and these include vessel dilatation, microaneurysm formation, and vessel leakage. Such conditions as retinal vein occlusion and the hyperviscosity syndrome share the retinal features of DR, but blood flow is reduced. The only similarity is that the pathologic diabetic retina is hypoxic. The increased flow in diabetes is, therefore, a paradox, but, as discussed above, the endothelial cell damage that may result from it could lead from what was originally a hyperperfused state to capillary closure and a hypoxic retina.

It has also been proposed that one reason DR progresses in pregnancy is rapid improvement in glycemia control over a short period of time. Phelps et al found a significant correlation between level of improvement achieved and the degree of DR progression, and several other studies have also found an association between rapid improvement of glycemia control and DR progression. In the present study, patients whose DR progressed experienced improvement that was similar to those whose DR remained unchanged. Both groups had good and comparable levels of glycemia control at the start of pregnancy. Those who suffered greatest progression in their DR status (n = 4) had poorer control at the start and achieved a greater degree of improvement than the group as a whole; the number involved was, however, too small for a more definite conclusion to be drawn.

Grunwald et al found that instillation of tight control reduces retinal blood flow, but interestingly those who did not undergo a reduction in flow were the ones who suffered a progression in their DR status. It is likely that those whose DR progressed had some factor(s) other than glycemia upon which retinal blood flow was dependent; these may include abnormal autoregulation and are likely to indicate that significant damage had already been incurred by the retinal vasculature. In the present study, the added stress of hyperperfusion led to increased flow in spite of improved control, possibly because of impaired autoregulation, with consequent deterioration in DR status.

We, therefore, propose that the worsening retinopathy seen during pregnancy is partly due to increased retinal blood flow induced by hyperperfusion. The diabetic retinal microcirculation, which may already be subject to increased flow, is unable to cope with the added stress, and there are deleterious consequences for the diabetic damage that may already exist. This effect on the DR status may be further compounded by the rapid achievement of better glycemia control. The results of this study further support the hypothesis that increased retinal blood flow plays an important role in the pathogenesis of DR.

**Key Words**

retinal blood flow, diabetic retinopathy, pregnancy, autoregulation
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