Effect of Pregnancy on Microvascular Complications in the Diabetes Control and Complications Trial

THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP

OBJECTIVE — To assess the effect of pregnancy on the development and progression of retinopathy and microalbuminuria in type 1 diabetes.

RESEARCH DESIGN AND METHODS — We conducted longitudinal analyses of the Diabetes Control and Complications Trial (DCCT), a multicenter controlled clinical trial that compared intensive treatment with conventional diabetes therapy, and studied 180 women who had 270 pregnancies and 500 women who did not become pregnant during an average of 6.5 years of follow-up. Women assigned to the conventional treatment group were changed to intensive therapy if they were planning pregnancy or as soon as possible after conception. Fundus photography was performed every 6 months, and the urinary albumin excretion rate (AER) was measured annually.

RESULTS — Compared with nonpregnant women, pregnant women had a 1.63-fold greater risk of any worsening of retinopathy from before to during pregnancy ($P < 0.05$) in the intensive treatment group; the risk was 2.48-fold greater for pregnant vs. not pregnant women in the conventional group ($P < 0.001$). In the conventional group, the odds of ≥3-step progression from the baseline retinopathy level was >2.9-fold among pregnant vs. not pregnant women ($P = 0.003$). The odds ratio (OR) peaked during the second trimester (OR = 4.26, $P = 0.001$) and persisted as long as 12 months postpregnancy (OR = 2.87, $P = 0.005$). The level of AER during pregnancy in the intensive group, but not in the conventional group, was significantly elevated from the level at baseline, albeit in the normal range. Although individual patients had transient worsening of retinopathy during pregnancy, even to the proliferative level, at the end of the DCCT, mean levels of retinopathy and albuminuria in subjects who had become pregnant were similar to those in subjects who had not become pregnant within each treatment group.

CONCLUSIONS — Pregnancy in type 1 diabetes induces a transient increase in the risk of retinopathy; increased ophthalmologic surveillance is needed during pregnancy and the first year postpartum. The long-term risk of progression of early retinopathy and albumin excretion, however, does not appear to be increased by pregnancy.

Diabetes Care 23:1084–1091, 2000

Controversy exists regarding the effects of pregnancy on the development and rate of progression of underlying retinopathy and nephropathy in patients with type 1 diabetes (1). Although many studies have suggested a worsening of retinopathy during pregnancy (2–8), others have not (9–11). In some cases, the worsening during pregnancy progressed to proliferative disease that required photocoagulation (2,4,8). In some cohorts reported previously, pregnancy-associated changes regressed after delivery (3,4,8). Whether there is any long-term harmful effect of pregnancy on the overall progression of retinopathy is uncertain; some controlled studies have demonstrated no long-term effect (12,13), whereas others have demonstrated a deleterious effect (16).

Worsening of preexisting diabetic nephropathy has also been reported during pregnancy, usually consisting of increased proteinuria and either a decline in or lack of the normal increase in glomerular filtration rate (GFR) during pregnancy (14–21). In most of these reports, patients had generally mild nephropathy with preservation of GFR, and pregnancy was not thought to alter the overall rate of progression substantially (13–15,17,19,21). However, in patients with an already decreased GFR, some reports (16–19), but not all (20,21), have shown that pregnancy appeared to accelerate nephropathy.

The mechanisms by which pregnancy might alter the course of these underlying complications have not been elucidated, but some studies found correlations between worsening of retinopathy with the degree of improvement of glycemic control obtained with the institution of intensive therapy that was performed before and during pregnancy (5,7,10). Whether the transient worsening of retinopathy during pregnancy is similar to that seen with the institution of intensive therapy (22–25) is not clear; however, rapid institution of intensive therapy during pregnancy has been suggested as the cause of worsening retinopathy (1).

Frequent measurements of the development of retinopathy and microalbuminuria in the Diabetes Control and Complications

A complete listing of the Diabetes Control and Complications Trial Research Group is available in *Archives of Ophthalmology* 113:36–51, 1995.

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Received for publication 28 December 1999 and accepted in revised form 2 May 2000.

Abbreviations: AER, albumin excretion rate; C_{Cr}, creatinine clearance; DCCT, Diabetes Control and Complications Trial Research Group; ETDRS, Early Treatment Diabetic Retinopathy Study; GEE, generalized estimating equation; GFR, glomerular filtration rate; I, improvement; OR, odds ratio; SNPDR, severe nonproliferative diabetic retinopathy; W, worsening.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline covariates related to diabetic complications*

Covariates*	Women who did not become pregnant	Women who became pregnant	
		Intensive	Conventional
n	500	94	86
Age (years)	27.1 ± 7.7*	24.2 ± 5.4	23.6 ± 5.8
Duration of diabetes (years)	5.6 ± 4.2	5.8 ± 4.5	6.7 ± 4.5
Adolescent (%) (<18 years of age)	12.8	11.7	14.0
Retinopathy† (%)			
No retinopathy	52.8	52.1	40.7
20/<20 (microaneurysms in one eye)	14.8	16.0	15.1
20/20 (microaneurysms in both eyes)	14.2	16.0	19.8
20/30–39 (mild nonproliferative retinopathy)	13.4	11.7	22.1
20/≥40 (moderate nonproliferative retinopathy)	4.8	4.3	2.3
AER (mg/24 h)	15.1 ± 17.5	19.4 ± 23.3	15.4 ± 11.1
≥40 mg/24 h (%)	4.6	9.6	3.5
Screening HbA_{1c}	9.2 ± 1.7	9.3 ± 1.7	9.1 ± 1.7
Weight (kg)	63.0 ± 9.2	62.4 ± 8.4	61.3 ± 9.2
Mean blood pressure (mmHg)	84.6 ± 8.2	85.0 ± 7.7‡	82.3 ± 7.8
History of urinary tract infection (%)	19.0	18.1	25.6
Prior pregnancy (%)	50.0§	40.4	34.9

Data are *n* or means ± SD, unless otherwise indicated. *$P < 0.001$ vs. women who became pregnant during the DCCT; †graded according to modified ETDRS classification (25); ‡$P = 0.02$ vs. conventional treatment group; §$P = 0.005$ vs. women who became pregnant during the DCCT.

Trial (DCCT) have allowed us to reexamine whether pregnancy alters the initial development or subsequent progression of these complications. Furthermore, the experimental design of the study, which included mandatory rapid intensification of therapy in those women in the conventional treatment group in preparation for or during pregnancy, allowed us to examine whether any changes in retinopathy were due to pregnancy itself or to the rapid institution of intensive therapy for pregnancy.

RESEARCH DESIGNS AND METHODS

The DCCT was designed to assess the effects of intensive diabetes treatment on the development and progression of the microvascular complications of diabetes but not specifically to examine the effects of pregnancy (24). However, an ancillary study was implemented in 1990 to capture more data on the pregnancies of the women enrolled in the DCCT (26).

Study subjects

All subjects recruited into the DCCT were 13–39 years of age, had type 1 diabetes for 1–15 years, and were in generally good health. Women who were pregnant or who planned or desired a pregnancy within 2 years of the time of randomization were excluded (24).

Subjects were randomly assigned to conventional therapy or to an intensive treatment regimen aimed at achieving glycemic levels as close to the nondiabetic range as safely as possible (24). Women assigned to the conventional treatment group were changed to intensive therapy if they were planning pregnancy or as soon as possible after conception. There were 86 women in the conventional treatment group who became pregnant during the DCCT. They all resumed conventional therapy after delivery or termination of the pregnancy. In the group assigned to intensive therapy, 94 women became pregnant. Details regarding other aspects of these pregnancies, including their outcomes, have been reported (26).

Assessment of retinopathy, renal function, and glycemic control

Fundus photography was performed every 6 months throughout the study. During pregnancy, there were additional visits to the ophthalmologist each trimester, but additional photographs were not taken unless clinically indicated. Retinopathy progression was defined as a higher grade of retinopathy on the final Early Treatment Diabetic Retinopathy Study scale of retinopathy severity (25) by at least 1, 2, or 3 steps from the grade at baseline (before randomization) or from the grade at the most recent evaluation prepregnancy.

Assessments of renal function were carried out on a yearly basis and consisted of an assessment of urinary albumin excretion rate (AER) and calculation of a creatinine clearance (C_{Cr}) based on a 4-h collection and serum creatinine (24). Chronic glycemic control was measured quarterly in all subjects before pregnancy and monthly during pregnancy with a central high-performance liquid chromatography assay of HbA_{1c} (24). Microalbuminuria was considered present if AER was ≥40 mg/24 h (28 μg/min) as previously defined (24).

Pregnancy status

The date of conception was estimated to be 28 days before the date that pregnancy was diagnosed. The length of pregnancy was computed as the time elapsed from the date of conception to the date of delivery or termination of pregnancy. At each complication assessment visit, the patients were classified as not pregnant; as in the first, second, or third trimester of pregnancy; or as in the period 0–6 months, 6–12 months, or >12 months after pregnancy. In the conventional treatment group, the status of those not pregnant was further classified as either not pregnant and therapy not changed for conception or as therapy changed to intensive therapy in preparation for conception.

Statistical methods

A Wilcoxon's rank-sum test was used to test for differences for quantitative or ordinal observations, or a χ^2 test was used for categorical data (27). All results nominally significant at $P < 0.05$ are cited.

The incidence of worsening (W) versus improvement (I) in the level of retinopathy during pregnancy was evaluated from the assessment immediately before the pregnancy versus the last assessment during the pregnancy. The difference in the paired proportions of W:I was compared using the McNemar test with multinomial-based large sample confidence limits. A stratified adjusted McNemar test was computed using the inverse variance weighted combination over strata (28). Likewise, the stratified-adjusted conditional odds ratio (OR) and confidence limits were computed (28). Spearman rank correlations (27) were computed for the change in grade of retinopathy and the change in AER for before to during pregnancy versus the change in HbA_{1c}.

Generalized estimating equation (GEE) logistic regression models (29) were used to assess the log odds of recent progression in retinopathy between pregnant versus nonpregnant women. The prepregnancy visit to assess retinopathy occurred 6 months previously for some women, and 12 months previously for those with 2 successive fundus photographs during pregnancy. Thus, the analysis included changes from both the 6-month previous visit and the 12-month previous visit for all women who became pregnant. Time-dependent covariates included whether the current visit occurred while a woman was pregnant versus not pregnant, the recent change in HbA_{1c} from the previous visit, the time of the current visit, and the level of retinopathy at the previous visit.

GEE analyses for quantitative variables assessed the change in the log AER from before to during pregnancy, which can be expressed as the percent change in AER, adjusted for the recent (last annual) log AER 12 months prior.

The prevalence of retinopathy progression was described using simple proportions with ≥3-steps worse retinopathy from the level at baseline at all outcome assessment visits while a woman was in each pregnancy state (e.g., all 6 monthly retinopathy assessments performed during the first trimester). The effect of pregnancy status on the risk (log OR) of retinopathy progression was assessed by GEE regression models using time-dependent binary covariates for the current pregnancy status classification of each woman, which were adjusted for the baseline level of retinopathy and other factors. The reference category was "not pregnant" in the intensive group or "not pregnant and not changed to intensive therapy" in the conventional treatment group. Similar analyses assessed the difference between women pregnant versus not pregnant with respect to the percent change in the AER from baseline, adjusting for the baseline AER and other factors.

RESULTS

General characteristics of women who became pregnant during the DCCT

Pregnancy during the DCCT. Among the 345 women in the intensive treatment group, 94 women had 135 pregnancies during the DCCT. Among the 335 women in the conventional treatment group, 86 women had 135 pregnancies. Of these 86 women, 64 changed to intensive therapy when preparing for conception (113 pregnancies) over an average of 8.2 months (range 0.03–86). The remaining 22 women in the conventional treatment group changed to intensive therapy only after becoming pregnant (22 pregnancies). A full description of the maternal and fetal outcomes, extent of follow-up, adherence to assigned treatment, and the glycemic and obstetric management of the 270 pregnancies in these 180 women, whose pregnancies occurred between August 1983 and June 1993, has been reported (26). Of the retinal and the renal evaluations, 92 and 91%, respectively, were conducted during pregnancy as scheduled.

Baseline and time-dependent covariates. Those women who became pregnant during the DCCT and those who did not had similar baseline characteristics, except for age, blood pressure, and a history of prior pregnancy before the trial (Table 1). The distributions of $HbA_{1c,}$ weight, and mean blood pressure during each pregnancy state for each treatment group are shown in Table 2. In both treatment groups, mean HbA_{1c} decreased during pregnancy and gradually returned to the prepregnancy level after delivery. Body weight increased during pregnancy and blood pressure decreased during the first 2 trimesters.

Table 2—*Glycemic control, weight, and blood pressure for different pregnancy states*

	*n**	Current HbA_{1c} (%)	Weight (kg)	Blood pressure (mmHg)
Intensive treatment group				
Not pregnant	3,422	7.3 ± 1.2	68.9 ± 11.1	85.7 ± 8.5
During pregnancy				
First trimester	54	7.0 ± 1.2	69.1 ± 10.1	82.8 ± 8.1
Second trimester	41	6.2 ± 0.7	70.9 ± 8.5	82.4 ± 8.6
Third trimester	37	5.9 ± 0.7	76.9 ± 9.8	86.2 ± 7.9
After pregnancy				
0–6 months	119	7.0 ± 1.2	69.3 ± 9.7	84.6 ± 8.6
6–12 months	105	7.2 ± 1.0	69.1 ± 10.3	83.3 ± 8.4
>12 months	373	7.3 ± 1.1	70.6 ± 12.0	84.4 ± 8.0
Conventional treatment group				
Not pregnant	3,397	9.4 ± 1.6	65.4 ± 10.0	85.1 ± 8.7
Changed to intensive therapy for conception	46	7.3 ± 1.2	62.8 ± 7.7	85.7 ± 6.4
During pregnancy				
First trimester	49	7.3 ± 1.6	63.9 ± 6.5	84.5 ± 9.2
Second trimester	46	6.0 ± 1.0	70.3 ± 9.9	81.2 ± 9.6
Third trimester	39	5.9 ± 0.7	75.1 ± 8.5	86.5 ± 9.7
After pregnancy				
0–6 months	106	7.6 ± 1.8	65.5 ± 7.6	85.4 ± 8.8
6–12 months	87	8.4 ± 1.5	64.6 ± 8.2	85.2 ± 8.4
>12 months	262	8.8 ± 1.5	66.3 ± 7.0	84.4 ± 7.9

Data are *n* or means ± SD. *Number of semi-annual visits for retinopathy.

Retinopathy

Incidence of recent retinopathy progression. Table 3 compares incidence of short-term progression of retinopathy between women who became pregnant versus those who did not, adjusting for temporal effects. Within the conventional treatment group, recent progression was observed at 51% (37 of 73) of visits while pregnant, compared with 31% among all visits while not pregnant. The estimated OR is 2.48, adjusted for the prior level of retinopathy ($P < 0.001$). Likewise, in the intensive treatment group, progression was observed in 31% of visits while pregnant compared with 23% while not pregnant (adjusted OR = 1.63, $P < 0.05$). These ORs were unchanged after adjustment for the recent change in HbA_{1c}.

Prevalence of worse retinopathy from the level at baseline. In addition to the analyses of incidence of any worsening of retinopathy during pregnancy, which may not be clinically meaningful, we also assessed worsening by ≥3 steps beyond the level at DCCT baseline.

For each pregnancy state (not pregnant, pregnant, and various times postpar-

Table 3—*Comparison of incidences of short-term progression of any retinopathy between pregnant and nonpregnant women**

Group	Not pregnant Total	Not pregnant With worse retinopathy	Pregnant Total	Pregnant With worse retinopathy	OR†	95% CI	*P*
Intensive							
Unadjusted	2,950	693 (23)	124	39 (31)	1.62	1.01–2.59	<0.05
Adjusted‡	—	—	—	—	1.63	1.01–2.64	<0.05
Conventional							
Unadjusted	5,605	1,742 (31)	73	37 (51)	2.54	1.59–4.03	<0.001
Adjusted	—	—	—	—	2.48	1.56–3.94	<0.001

Data are *n* or *n* (%), unless otherwise indicated.*Progression is relative to the pregnancy-free ETDRS level 6 and 12 months prior; †OR obtained from a GEE logistic regression model; ‡model adjusted for the prepregnancy retinopathy status, the recent change in HbA_{1c} from the prior visit, and time of visit during study.

tum), Table 4 presents the number of retinopathy assessment visits, and Table 5 presents the number and percent of visits at which ≥3-steps worse retinopathy was present. In the conventional treatment group, among those 3,390 visits in which a woman was not pregnant (and not yet changed to intensive therapy for conception), 451 (13.3%) showed worse retinopathy by ≥3 steps. Among the 135 visits during pregnancy, 23 showed worse retinopathy (17%) for a crude relative risk of 1.28. The prevalence of worse retinopathy observed at the different periods after pregnancy also tended to be higher than at visits when women were not pregnant. Although the numbers are small, the rates of worse retinopathy during each trimester (6 of 50, 11 of 46, and 6 of 39) suggest a possible peak during the second trimester.

Within the intensive treatment group, worse retinopathy was observed in 8 of 132 (6.1%) of the visits during pregnancy, which is not an adequate number to assess risk by trimester. This crude risk was only slightly greater than that among visits while not pregnant (5.7%). During and after pregnancy, the prevalence in the conventional treatment group was higher than that observed in the intensive treatment group.

Table 5 also presents GEE logistic regression model estimates of the OR of worse retinopathy by ≥3 steps from baseline in each treatment group; data are adjusted for the effects of time of visit since baseline, baseline retinopathy status, age, duration of diabetes at baseline, screening HbA_{1c}, and the current mean HbA_{1c}. In the conventional treatment group, the 40 women evaluated after having changed to intensive treatment, but before becoming pregnant, had a risk of retinopathy progression (OR = 1.56) similar to women who had not yet changed to intensive therapy or become pregnant. However, among the 135 evaluations conducted during pregnancy, the odds of worse retinopathy were increased 2.9-fold (P = 0.003) and had peaked during the second trimester (OR = 4.26, $P < 0.001$). This increased risk persisted for the first year after pregnancy, with the highest postpregnancy risk occurring during the first 6 months postpartum (OR = 3.16, $P < 0.001$).

Within the intensive treatment group, the model is not reliable owing to the small numbers of patients with worse retinopathy during pregnancy. However, the risks during and after pregnancy were not as greatly increased in this group as in the conventional group for any pregnancy state. The greatest increase in risk in the intensive group was observed during the first 6 months after pregnancy (OR = 1.54, NS).

Five subjects in the intensive treatment group and 8 in the conventional treatment group developed severe retinopathy changes; 3 subjects in the conventional treatment group required laser photocoagulation. In 9 of these 13 cases, retinopathy progressed even further postpartum before it improved. In only one of these cases was proliferative disease present before pregnancy. One patient who only had microaneurysms bilaterally before pregnancy progressed to proliferative disease during pregnancy. She returned to a microaneurysm-only state by 1 year after pregnancy.

Effects of change to intensive therapy in the conventional treatment group. Additional analyses in the conventional treatment group assessed the effects of changing to intensive therapy before pregnancy versus after the onset of pregnancy. Among women who had waited to change to intensive therapy until after becoming pregnant, 17 of 93 assessments showed worsening of retinopathy during pregnancy, with an OR of 2.1 vs. nonpregnant women (P = 0.03), adjusted for baseline retinopathy status, age, diabetes duration, screening HbA_{1c}, history of pregnancy before the DCCT, and time of visit during study. Among women who had changed to intensive therapy before pregnancy, 6 of 42 assessments showed worse retinopathy with an adjusted OR of only 0.9 versus nonpregnant women. Although there appears to be greater risk of worsening during pregnancy among those women who had not changed to intensive therapy before pregnancy versus those who had changed to intensive therapy, the difference (2.1 vs. 0.9) was not statistically significant (P = 0.11). For the postpartum period, the OR was 1.7 among those who changed before pregnancy and 2.0 among those who did not.

Effects of rapid improvement of glycemic control on worsening of retinopathy. Table 6 describes the effect of the rapid

Table 4—*Number of retinopathy visits during each pregnancy state*

Treatment	Not pregnant during DCCT	Deviation for conception	During Pregnancy	After pregnancy 0–6 months	After pregnancy 6–12 months	After pregnancy >12 months
Intensive treatment						
Total visits	3,422	—	132	119	105	373
Visits with event	195	—	8	11	8	21
% with event	5.7	—	6.1	9.2	7.6	5.6
Conventional treatment						
Total visits	3,390	40	135	112	89	266
Visits with event	451	5	23	22	17	45
% with event	13.3	12.5	17.0	19.6	19.1	16.9

Data are *n* or %.

Table 5—*OR of ≥3-step retinopathy progression from baseline level during each pregnancy state*

	Intensive treatment*			Conventional treatment†		
Pregnancy state	OR	95% CI	*P*	OR	95% CI	*P*
Changed to intensive therapy before conception but not yet pregnant‡	—	—	—	1.56	0.53–4.56	NS
Pregnant vs. not pregnant	1.37	0.56–3.33	NS	2.90	1.45–5.82	0.003
First trimester	—	—	—	1.93	0.57–6.61	NS
Second trimester	—	—	—	4.26	2.05–8.88	<0.001
Third trimester	—	—	—	2.56	0.91–7.26	NS
After pregnancy						
0–6 months	1.54	0.81–2.95	NS	3.16	1.61–6.19	<0.001
6–12 months	1.38	0.65–2.90	NS	2.87	1.37–6.01	0.005
>12 months	0.65	0.31–1.36	NS	1.19	0.60–2.40	NS

Data are adjusted for time in study, baseline retinopathy status, age, duration of diabetes, screening HbA_{1c}, history of pregnancy, prior # DCCT, and current mean HbA_{1c}. *OR versus not pregnant; †OR versus not pregnant and not changed to intensive therapy in preparation for conception; ‡unadjusted for first, second, or third trimester.

improvement in glycemic control on the incidence of recent worsening of retinopathy. Of the intensively treated patients, 80% improved their HbA_{1c} levels during pregnancy, usually to a modest degree. Of the conventionally treated patients, 95% improved their HbA_{1c} levels, usually quite considerably. In both groups, there was an overall significantly greater odds of worsening of retinopathy during pregnancy by >2-fold that persisted after adjusting for the magnitude of the change in HbA_{1c}. In the conventional group, but not the intensive group, there also was a significant rank correlation ($P < 0.05$) between the change in retinopathy and the change in HbA_{1c}, with a greater degree of worsening retinopathy accompanying greater decreases in HbA_{1c} levels.

AER

The low frequencies of short-term recent progression from normal to microalbuminuria and of short-term doubling of AER during pregnancy precluded analyses of these outcomes. Thus, we assessed the recent change in the value of the log AER as a continuous variable over each successive year in study. In the combined intensive and conventional treatment groups, the average yearly change in AER between annual visits was 3.77% for the 7,681 successive annual AER evaluations while a woman was not pregnant (data not shown). Among the 138 women who had an AER evaluated during their first pregnancy, the mean percent change from the pre-pregnancy evaluation 1 year prior was 4.17%. There was a slightly greater change in the intensive group during pregnancy, but the recent change in AER was not statistically significantly different within either treatment group.

We also conducted an analysis of the percent change in AER during each pregnancy state from the baseline value at entry into the study, which was analogous to the analysis of retinopathy in Table 4. The change in AER from baseline was used because there were only 10 instances of the onset of microalbuminuria (≥40 mg/24 h) during pregnancy in the study.

In the conventional treatment group, the geometric mean percent change from baseline was 13% among the 1,734 AER evaluations performed while a woman was not pregnant. In contrast, the mean percent change in AER from 29 visits during a period of change to intensive therapy before pregnancy, from 69 visits during pregnancy, and from 67 visits during the first 6 months after pregnancy was −15, 12, and 79%, respectively. From a GEE regression model, the overall AER during pregnancy (relative to the baseline value) was not significantly greater than that among women who had yet to become pregnant (1.19-fold greater) or during each trimester, although it peaked at 1.57-fold greater during the third trimester (adjusted for time in study, baseline AER, and current mean HbA_{1c}). AER during the first 6 months after pregnancy was 1.84-fold greater than that among women who had yet to become pregnant ($P < 0.001$).

A similar trend was observed in the intensive treatment group. The geometric mean percent change from baseline was −11% among the 1,744 AER evaluations while a woman was not pregnant. From a GEE regression model, the adjusted AER relative to baseline during pregnancy was 1.36-fold greater than that among women who had yet to become pregnant ($P < 0.02$) and also peaked at 1.59-fold greater during the third trimester ($P < 0.02$). Adjusted AER relative to baseline during

Table 6—*Change in retinopathy during pregnancy* (adjusted for change in HbA_{1c})*

	n	% Worse	% Better	OR	95% CI	*P*
Intensive						
Unadjusted	77	40	18	2.2	1.2–4.2	<0.012
Adjusted for change in HbA_{1c}						
HbA_{1c} increased	15	40	33	1.2	0.4–3.9	NS
$0.0\% < HbA_{1c}$ decrease $\leq 0.7\%$	20	50	25	2.0	0.7–5.9	NS
$0.7\% < HbA_{1c}$ decrease $\leq 1.3\%$	22	27	5	6.0	0.7–50.0	NS
$1.3\% < HbA_{1c}$ decrease	20	45	15	3.0	0.8–11.1	NS
Stratified-adjusted†	—	—	—	2.1	1.1–4.0	<0.006
Conventional						
Unadjusted	74	53	15	3.5	1.8–6.9	<0.001
Adjusted for change in HbA_{1c}						
HbA_{1c} increased	4	0	0	—	—	—
$0.0\% < HbA_{1c}$ decrease $\leq 1.7\%$	23	35	30	1.1	0.4–3.2	NS
$1.7\% < HbA_{1c}$ decrease $\leq 3.1\%$	24	50	8	6.0	1.3–26.8	<0.008
$3.1\% < HbA_{1c}$ decrease	23	82‡	9	9.5	2.2–40.8	<0.001
Stratified-adjusted†	—	—	—	2.9	1.4–5.9	<0.001

*Change in retinopathy status and HbA_{1c} from before the first pregnancy to during the last retinopathy visit of the first pregnancy; †stratified-adjusted by HbA_{1c} subgroup; ‡$P < 0.05$ for rank correlation between change in retinopathy with change in HbA_{1c}.

Table 7—*Risk of complications among women at the end of the study according to treatment group and pregnancy status during the DCCT*

	Not pregnant		Pregnant				
Status at close-out	Total subjects	Events	Total subjects	Events	OR	95% CI	*P*
Retinopathy							
≥3-Steps worse							
Intensive	249	28 (11.2)	94	9 (9.6)	0.84	0.38–1.84	NS
Conventional	246	74 (30.1)	84	22 (26.2)	0.82	0.47–1.44	NS
SNPDR							
Intensive	249	4 (1.6)	94	2 (2.1)	1.33	0.24–7.39	NS
Conventional	246	20 (8.1)	84	6 (7.1)	0.87	0.34–2.24	NS
Nephropathy*							
Microalbuminuria							
Intensive	242	13 (5.4)	85	4 (4.7)	0.87	0.28–2.74	NS
Conventional	235	19 (8.1)	83	11 (13.2)	1.74	0.79–3.82	NS
Albuminuria							
Intensive	242	2 (0.8)	85	0 (0.0)	—	—	—
Conventional	235	4 (1.7)	83	1 (1.2)	0.70	0.08–6.39	NS

Data are *n* or *n* (%). *Women with baseline AER ≥40 mg/24 h were excluded from the analysis.

the first 6 months after pregnancy was 2.05-fold greater than that at comparable points in follow-up among women not yet pregnant ($P < 0.001$); the adjusted AER was 1.52-fold greater during months 6–12 postpartum ($P < 0.001$) and 1.18-fold after 1 year postpartum ($P < 0.02$).

For both groups, the majority of the values of AER were within the normal range at baseline. Thus, these small changes during or after pregnancy were within the normal range for most patients.

Complication status at end of study

To assess if pregnancy adversely affected the status of complications in the long term, we compared the end-of-study status of women who became pregnant during the DCCT to that of women who did not become pregnant during the DCCT. Table 7 shows that within each treatment group, pregnancy had no effect on the end-of-study prevalence of retinopathy or albuminuria.

Among the women who became pregnant during the DCCT, 12 had microalbuminuria at entry to the study (9 in the intensive treatment group and 3 in the conventional treatment group). None of these women developed clinical albuminuria. Only 1 patient in each group still had microalbuminuria at the end of the study. The remainder all had AER values <40 mg/24 h.

CONCLUSIONS — The DCCT is the first large prospective study to assess the effect of pregnancy on the development and progression of diabetic retinopathy and microalbuminuria. The DCCT women were generally younger, had shorter duration of diabetes, and had fewer and/or less severe complications than patients in virtually all other studies that have examined the effects of pregnancy on diabetic complications. In the women in the intensive treatment group, HbA_{1c} was in the normal or near-normal range for an average of 3 years before conception. Therefore, the DCCT cohort was less affected by known risk factors for the development or progression of retinopathy and/or albuminuria.

Retinopathy

Our data clearly show that in both treatment groups, there was a short-term increase in the level of retinopathy during pregnancy that persisted into the first year postpartum; the conventional group was somewhat more affected by pregnancy than the intensive group (Table 3). In the conventional treatment group, the 2.5-fold increase in the risk of retinopathy progression, compared with recent changes among nonpregnant women, was highly significant and was not altered by adjustment for temporal trends and other factors (Table 3). In the intensive treatment group, these adjusted risks were not as great, although the risk of retinopathy progression was nominally statistically significant. The analyses in the intensive treatment group are less reliable because of the markedly reduced overall incidence of worsening among intensively treated patients.

A further analysis (Table 4) comparing pregnant with nonpregnant women showed an increased and statistically significant risk of ≥3-step progression of retinopathy from the level at baseline in the conventional treatment group but not in the intensive treatment group (again owing to a small number of events). In the conventional treatment group, the risk peaked during the second trimester and persisted for a full year postpartum.

Of the patients who developed a 3-step progression with pregnancy, 5% progressed to stages of proliferative retinopathy or severe nonproliferative retinopathy, and 3 patients required laser photocoagulation during pregnancy. Progression to proliferative retinopathy with a need for photocoagulation has been reported previously in similar proportions of patients (6–9). In the current study, progression often continued into the postpartum period, sometimes requiring photocoagulation after delivery. Although postpartum progression has been noted previously (30), it has not resulted in a change in clinical practice (1,3,11,31). The persistent effect of pregnancy on retinopathy risks requires continued frequent ophthalmologic surveillance for the first year postpartum.

The proportion of women with short-term progression of retinopathy during pregnancy in the intensive group was not as great as that in the conventional group. However, the finding of a trend toward short-term worsening in the intensive treatment group (Table 3) suggests that the effect of pregnancy was superimposed upon that of long-term metabolic control.

In the conventional treatment group, there was a significant trend toward greater worsening of retinopathy among those with greater reductions in HbA_{1c} (Table 7). This trend suggests that some of the short-term worsening in the conventional treatment group may be related to the early worsening phenomenon, which in turn has been shown to be related to the magnitude of the decrease in HbA_{1c} levels with implementation of intensive diabetes treatment (22–25). However, when recent changes in retinopathy were compared between pregnant and nonpregnant women and were adjusted for the recent change in HbA_{1c}, the increased worsening of retinopathy during pregnancy persisted.

There did not appear to be any worsening of retinopathy in women in the con-

ventional treatment group during the period of conversion to intensive therapy before conception, although the sample size was small. Among women in the conventional group who did not change to intensive therapy in preparation for pregnancy, the ORs for pregnancy-induced 3-step changes during or after pregnancy were increased compared with nonpregnant women, whereas these ratios were not increased for those who changed to intensive therapy in advance of the pregnancy. However, the comparison of the ORs for change in therapy before pregnancy with those for change in therapy after pregnancy did not reach statistical significance.

The follow-up examinations showed that the effects of pregnancy on retinopathy may continue to increase over the first year after pregnancy but eventually will diminish. More importantly, analysis of the end-of-study data suggested that the worsening of retinopathy during pregnancy had no long-term consequences. In accord with previous findings (12,13), women who did or did not become pregnant during the DCCT had similar retinopathy levels at the end of the study.

There were too few instances of the development of microalbuminuria during pregnancy to conduct reliable analyses of the effects of pregnancy on the risks of microalbuminuria or clinical albuminuria. Thus, analyses addressed the presence of any worsening versus improvement of AER during pregnancy and the percent change in the level of AER over time. Like retinopathy, there was a trend toward an increase in AER from before to after pregnancy in both treatment groups. When the change in AER from the level at baseline was compared between pregnant and nonpregnant women, a greater increase in AER during pregnancy was observed in the intensive but not in the conventional treatment group. Both treatment groups showed greater increases in the AER after pregnancy, more so in the intensive than in the conventional treatment group. Again, these changes in AER appeared to be a function of pregnancy.

The adverse effect of pregnancy on albumin excretion was relatively transient, as has been shown previously (13–15). Importantly, pregnancy did not have a long-term effect on the ultimate development of diabetic nephropathy, as judged by the end-of-study findings where similar proportions of women developed microalbuminuria, regardless of whether they had been pregnant during the DCCT. Other studies have shown that in women with normal AERs or with renal disease limited to micro- or macroalbuminuria, pregnancy does not appear to accelerate the course of their nephropathy (13–15,19–21).

Several limitations should be noted. Regular assessments of retinopathy and renal function were performed on all participants, and scheduling was not adjusted for pregnancy. Thus, evaluations during pregnancy and after pregnancy varied greatly with respect to the week of gestation or the week postpartum. Also, for annual renal assessments and to a lesser extent, the semi-annual retinopathy assessments, the elapsed time between the assessments before, during, and after pregnancy varied. For some women, no renal assessments were obtained during a pregnancy simply because the pregnancy was completed over a 9-month period between 2 annual renal examinations. Therefore, these data may not be as reliable as those obtained from the systematic follow-up of a cohort of women planning pregnancy, with evaluations at fixed times during gestation and postpartum for all women.

In conclusion, the primary finding of our study is the demonstration that the pregnant state, rather than the institution of intensive diabetes treatment, is the primary cause of worsened diabetic retinopathy. Nonetheless, a minor effect of rapid improvement of glycemic control on worsening of retinopathy was seen. In addition, the adverse effect of pregnancy on retinopathy was greater in the conventionally treated group compared with the intensively treated group, showing that the effects of pregnancy are additive to the effects of poor metabolic control. The worsening of retinopathy during pregnancy can be quite significant, occasionally requiring photocoagulation during pregnancy, although in the DCCT, only 3 conventional treatment group patients required laser therapy.

Women with type 1 diabetes must be followed closely by an experienced retina specialist during pregnancy. This adverse effect of pregnancy on retinal status persists into the first year postpartum, and increased retinal surveillance by a retina specialist should be continued during the first year. Fortunately, the effect of pregnancy is relatively transient; most changes revert to prepregnancy levels after a year or more.

Our data suggest that in the setting of intensive therapy during pregnancy, pregnancy does not affect the ultimate long-term rate of progression of underlying mild-to-moderate retinopathy or very early nephropathy.

Acknowledgments — The DCCT was sponsored by the Division of Diabetes, Endocrinology and Metabolic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institutes of Health, through cooperative agreements and a research contract. Additional support was provided by the National Heart, Lung and Blood Institute, the National Eye Institute, and the National Center for Research Resources through the General Clinical Research Centers Program.

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