ELSEVIER

Pregnancy Does Not Induce or Worsen Retinal and Peripheral Nerve Dysfunction in Insulin-Dependent Diabetic Women

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ABSTRACT

In order to verify whether pregnancy induces or worsens diabetic retinopathy or somatic and autonomic neuropathy, 16 insulin-dependent diabetic (IDDM) pregnant women, 14 age-matched nondiabetic pregnant women, and 12 IDDM nonpregnant women matched for age and disease duration were studied. Plasma glucose, HbA_{1c}, and fructosamine were repeatedly assayed during pregnancy. Retinopathic and neuropathic endpoints were evaluated through ophthalmoscopy, electrophysiology of left peroneal and sural nerves (motor and sensory conduction velocities), and cardiovascular autonomic tests (deep breathing, cough test, lying-to-standing). In the IDDM pregnant women, evaluations were performed three times during pregnancy and 6 months after delivery. Good metabolic control was achieved during pregnancy. At baseline, nine IDDM pregnant women did not show signs of retinopathy, and seven had nonproliferative retinopathy. Only one patient showed worsening during pregnancy, but she improved after delivery. Motor conduction velocity, significantly lower in IDDM pregnant women, progressively improved, and, in the third trimester, was not significantly different from that of nondiabetic pregnant women. At baseline, none of the IDDM pregnant women had abnormal responses to cardiovascular autonomic tests. During pregnancy, the response to deep breathing appeared temporarily reduced in all pregnant women, possibly due to lowered ventilatory excursion at the end of pregnancy. In IDDM women with minimal or no retinopathy, and subclinical or no peripheral neuropathy, pregnancy does not appear to induce or worsen these complications. (Journal of Diabetes and Its Complications 12;2:74–80, 1998.)

INTRODUCTION

Diabetes mellitus in pregnancy is known to have negative effects on both mother and infant.[1–4] In the last few decades, insulin therapy and very close monitoring of diabetic women during pregnancy, aiming at optimal metabolic control, has reduced perinatal mortality and congenital malformation rates.[5,6] Although pregnancy is no longer ''out'' for diabetic patients with chronic complications,[7] the effects of pregnancy on such complications are still unclear.[8,9] Only limited data are available on the effects of pregnancy on retinopathy and peripheral somatic or autonomic neuropathy.[10–18] We therefore believed it would be of interest to verify whether pregnancy induces or worsens long-term diabetic complications. For this purpose, a group of insulin-dependent diabetic (IDDM) patients was followed during and after pregnancy and compared with groups of normal pregnant women and nonpregnant IDDM women.

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METHODS

Sixteen pregnant IDDM women, 29 ± 4.7 yrs old (mean ± SD) and with a disease duration of 11.2 ± 7.1 years were studied: pregnancy was diagnosed within the eighth gestational week. Fourteen age-matched (29.2 ± 3.8 years) pregnant women with no family history of diabetes and with normal glucose tolerance, and 12 IDDM women, matched for age (29 ± 7.3 yrs) and disease duration (12.8 ± 6.8 years), randomly chosen from among our outpatients, represented control groups.

Unless otherwise specified, the metabolic and instrumental end-points of the pregnant women were recorded at each trimester of pregnancy (first, second, third); the pregnant IDDM patients were also examined 6 months after delivery. Non-pregnant IDDM patients were examined at baseline only.

Metabolic and Obstetric Management. In our Diabetic Clinic, management of diabetic pregnant women is undertaken by a team composed of a diabetologist, an obstetrician, and a dietician. Patients come to the Diabetic Clinic every 2 weeks for a metabolic check-up and insulin therapy. In our IDDM pregnant women, fasting and postprandial plasma glucose and fructosamine levels were measured every 2 weeks and HbA_{1c} levels every 2 months; patients also monitored their glucose levels four to six times daily with glucometers at home.

The aim of treatment was to achieve euglycemia as early as possible. Patients were managed by either continuous insulin infusion pumps or intensified subcutaneous insulin injections (four per day). They were followed by the obstetrician with periodic hormonal, fetal survey, and ultrasound examinations until delivery.

At expected term, patients were admitted to the Obstetric Department of Padova Hospital. At term, delivery was planned unless obstetric problems (preeclampsia, premature rupture of membrane, premature labor, major macrosomia, intrauterine growth retardation) or metabolic complications (hypertension, poor metabolic control) arose. Vaginal delivery was the first choice, but cesarean section was performed if the situation required it. At the moment of birth, a neonatologist evaluated the presence and severity of any malformations or perinatal morbidity. On the basis of infant birth weight, gestational age, and gender, each infant birth weight was calculated and expressed in percentiles: large for gestational age (LGA) greater than 90th percentile; small for gestational age (SGA), less than 10th percentile.

Retinopathy. Each patient underwent a complete ophthalmologic examination including best corrected visual acuity, measurement of intraocular pressure, anterior segment biomicroscopy, and fundus examination. Indirect and direct ophthalmoscopy and fundus photography were performed after mydriasis induced with tropicamide 1%. Retinopathy was classified according to Early Treatment Diabetic Retinopathy Study (ETDRS) criteria.[19]

Peripheral Neuropathy. Clinical assessment of peripheral neuropathy (positive and negative symptoms, signs) was made by means of a 39-item questionnaire covering sensory, motor, and autonomic features, and the Neurologic Disability Score.[20,21]

Somatic neuropathy was assessed by calculating the motor conduction velocity (MCV) and amplitude of the compound muscle action potential of the left peroneal nerve. Needle electromyography of the extensor digitorum brevis muscle provided additional information on muscle denervation. The antidromic sensory conduction velocity (SCV) of the left sural nerve was also measured.[22] According to normal age-matched values for our laboratory, MCV and SCV were considered abnormal at less than 42.3 m/sec and less than 40.6 m/sec, respectively. Nondiabetic pregnant women underwent electrophysiological studies at the first and third trimesters of pregnancy.

Autonomic Neuropathy. Three cardiovascular reflex function tests were performed: deep breathing (DB), cough test (CT) and lying-to-standing (LS).[23,24]

Deep Breathing. While lying supine, subjects were asked to inhale and exhale maximally for 1 min at a rate of six breaths per min. DB was expressed by the EI ratio, between the mean of the three longest R-R intervals in expiration and the mean of the three shortest R-R intervals in inspiration.

Cough Test. While lying supine, subjects were asked to give three vigorous (maximal) coughs, evenly spaced over 3 sec. The cough-induced HR response was expressed by the CT ratio, between the baseline R-R interval (mean of ten beats just before coughing) and the shortest R-R interval in the first 12 sec after coughing.

Lying-to-Standing. After lying quietly for 3 min, subjects were asked to rise quickly ($\leqslant$ 5 sec) and to stand still. This response was expressed by the ratio of the longest R-R interval from beat 25 to beat 35 and the shortest R-R interval from beat 10 to beat 20, from the onset of standing (LS 30/15 ratio).

Metabolic Evaluations. Fasting and postprandial plasma glucose levels were evaluated with a glucose oxidase method.[25] HbA_{1c} was measured by a microchromatographic method.[26] Fructosamine was evaluated colorimetrically.[27]

Statistical Evaluations. Comparisons between and within groups were carried out using Student's unpaired and paired *t*-test. The Wilcoxon signed-rank test

TABLE 1. METABOLIC PARAMETERS (MEAN ± SD) EVALUATED IN (A) 16 INSULIN-DEPENDENT DIABETIC PREGNANT WOMEN, (B) 14 NONDIABETIC PREGNANT WOMEN, AND (C) 12 INSULIN-DEPENDENT DIABETIC NONPREGNANT WOMEN

Parameters		Trimester of Pregnancy			
		First	Second	Third	Postpartum
Fasting plasma glucose (mg/*dl*)	A	143 ± 44[c,f]	117 ± 38[b,g,i]	108 ± 29[b,g,h]	135 ± 51[e]
	B	76 ± 11	79 ± 11	76 ± 10	—
	C	194 ± 70	—	—	—
HbA_{1c} (%)	A	7.2 ± 1.6[c,d]	6.0 ± 0.7[b,g,j]	6.4 ± 0.8[b,g]	7.4 ± 1.9
	B	5.1 ± 0.6	5.0 ± 0.3	5.1 ± 0.1	—
	C	8.8 ± 2.6	—	—	—
Fructosamine (mmol/L)	A	3.1 ± 0.6[c,d]	2.6 ± 0.3[c,g,h]	2.2 ± 0.3[a,g,k]	3.1 ± 0.8[d]
	B	1.8 ± 0.3	1.7 ± 0.18	1.75 ± 0.1	—
	C	3.8 ± 0.8	—	—	—

[a] $P < 0.05$; [b] $P < 0.005$; *and* [c] $P < 0.001$ *compared to B.*

[d] $P < 0.05$; [e] $P < 0.02$; *and* [f] $P < 0.01$, *and* [g] $P < 0.001$ *compared to C.*

[h] $P < 0.02$; [i] $P < 0.04$; [j] $P < 0.01$; *and* [k] $P < 0.001$, *A compared to First A.*

was used when the data did not appear to be normally distributed. Frequencies were assessed using the χ^2 method according to Yates' and Fisher's exact tests. Unless specified, data are expressed as means ± SD.

The IDDM nonpregnant women had only one evaluation for retinopathic and neuropathic endpoints, at baseline. This allowed direct comparison between groups at this time point, but rendered comparisons between groups for time courses unfeasible.

RESULTS

Weight and Metabolic Parameters. The IDDM pregnant women had body weights (BW) and body mass indexes (BMI, kg/m^2) which were not significantly different from those of nondiabetic pregnant women, at both the first (BW = 63.5 ± 9.4 versus 58.2 ± 8.2 kg; BMI = 24.4 ± 3.1 versus 22.2 ± 3.3) and third trimesters (BW = 72.2 ± 8.9 versus 67.4 ± 10.2; BMI = 27.8 ± 2.7 versus 25.7 ± 4.1; NS). The increase in BW was not significantly different between the two groups (8.6 ± 3.6 versus 9.4 ± 2.8).

Significantly higher values of fasting plasma glucose, HbA_{1c} and fructosamine were found in IDDM pregnant women compared to nondiabetic pregnant women, at all time points during the study (**Table 1**). However, the metabolic parameters did show a progressive and significant improvement during pregnancy, reaching near-normal values at the third trimester.

Significantly lower values of plasma glucose, HbA_{1c} and fructosamine were found in IDDM pregnant women compared to IDDM nonpregnant women (**Table 1**).

Retinopathy. Nine IDDM pregnant women (56%) showed no signs of retinopathy at baseline, during

TABLE 2. FREQUENCE OF RETINOPATHY, CLASSIFIED ACCORDING TO THE EARLY TREATMENT DIABETIC RETINOPATHY STUDY CRITERIA, IN 16 INSULIN-DEPENDENT DIABETIC PREGNANT WOMEN, 14 NONDIABETIC PREGNANT WOMEN, AND 11 INSULIN-DEPENDENT DIABETIC NONPREGNANT WOMEN

	Pregnant Women				Diabetic Nonpregnant Women	
	Nondiabetics		Diabetics			
	N	%	*N*	%	*N*	%
No retinopathy	14	100	9	56.3	6	55
Mild NPDR	—	—	5	31.2	1	9
Moderate NPDR	—	—	2	12.5	2	18
Moderately severe NPDR	—	—	—	—	1	9
PDR	—	—	—	—	1	9
Total	14	100	16	100	11	100

NDPR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

TABLE 3. MOTOR CONDUCTION VELOCITY (MCV) AND SENSOR CONDUCTION VELOCITY (SCV) VALUES (M ± SD) EVALUATED IN (A) 16 INSULIN-DEPENDENT DIABETIC PREGNANT WOMEN, (B) 14 NONDIABETIC PREGNANT WOMEN, AND (C) 12 INSULIN-DEPENDENT DIABETIC NONPREGNANT WOMEN

		Trimester of Pregnancy			
Parameters		**First**	**Second**	**Third**	**Postpartum**
MCV (m/sec)	A	42.8 ± 5.4[a,c]	43.9 ± 3.8[d]	45.4 ± 4.1[b,e]	43.3 ± 3.3
	B	46.9 ± 3.5	—	47.1 ± 4.8	—
	C	39.9 ± 4.3	—	—	—
SCV (m/sec)	A	46.2 ± 4.0[f]	45.0 ± 4.2	47.9 ± 5.8[g,h]	42.9 ± 4.2
	B	45.1 ± 4.6	—	45.6 ± 4.5	—
	C	41.8 ± 8.9	—	—	—

[a] $P < 0.03$ *versus third trimester.*

[b] $P < 0.05$ *versus postpartum.*

[c] $P < 0.03$ *versus B.*

[d] $P < 0.02$ *versus C.*

[e] $P < 0.003$ *versus C.*

[f] $P < 0.01$ *versus postpartum.*

[g] $P < 0.001$ *versus postpartum.*

[h] $P < 0.06$ *versus c.*

pregnancy, or in the 6 months after delivery. Seven patients (44%) showed signs of nonproliferative diabetic retinopathy at baseline, mild in five, and moderate in two cases. During pregnancy, this state worsened from mild to moderate in one patient, but regressed to mild after delivery. In one patient, moderate nonproliferative retinopathy was found to have progressed to severe 6 months after delivery.

Nondiabetic pregnant women had no signs of retinal vascular lesions at either examination. Six out of 11 IDDM nonpregnant women (55%) showed no signs of retinopathy; of the other five, one had mild, two moderate, and one moderate-severe nonproliferative retinopathy; one patient had had laser-treated proliferative retinopathy (**Table 2**). These values were not significantly different from those found in pregnant IDDM women.

Patients with retinopathy showed similar retinal lesions in both eyes.

Peripheral Neuropathy. No patient had symptoms or signs of peripheral neuropathy. MCV values were significantly lower in the IDDM than in the nondiabetic pregnant women in the first trimester, but then progressively improved in the third trimester ($P < 0.03$ from baseline), reaching values not very different from those of controls. This improvement was also observed in IDDM nonpregnant women. Although SCV values did not differ between groups during pregnancy, both MCV and SCV values worsened significantly 6 months after delivery in the IDDM pregnant women. No differences were observed between groups for amplitudes (**Table 3**).

Autonomic Neuropathy. No patient had abnormal cardiovascular autonomic function tests. No differences were observed among groups, except for LS (30/15) between IDDM and nondiabetic pregnant women. Deep breathing [exhale/inhale (EI) ratio] was significantly reduced in the third trimester in the two groups, but returned to baseline after delivery. The LS test showed a similar pattern in the IDDM pregnant women (**Table 4**).

Delivery. Regarding pregnancy outcome, IDDM pregnant women had a significantly higher frequency of cesarean sections than normal pregnant women (10 versus 2, $\chi^2 = 4.28$, $P < 0.05$). The number of SGA infants did not differ between the two groups, whereas there were significantly more LGA children in the diabetic group (five versus zero, $P < 0.02$). Preterm birth (gestation less than 37 weeks) occurred in three diabetic patients and in one control.

No congenital malformations were found in the children of diabetic mothers.

DISCUSSION

Whether pregnancy can induce or worsen chronic diabetic complications is still a controversial topic. In this study, we addressed this issue by looking at retinopathic and neuropathic end points during pregnancy.

Most of our IDDM patients, not having programmed their pregnancies, were not in a state of rigorous metabolic management prior to conception. However, they did come to our Diabetic Clinic as soon as they knew they were pregnant. During pregnancy, their metabolic control improved progressively and became optimal

TABLE 4. CARDIOVASCULAR TESTS (MEAN ± SD) EVALUATED IN (A) 16 INSULIN-DEPENDENT DIABETIC PREGNANT WOMEN, (B) 14 NONDIABETIC PREGNANT WOMEN, AND (C) 12 INSULIN-DEPENDENT DIABETIC NONPREGNANT WOMEN

		Trimester of Pregnancy			
Parameters		**First**	**Second**	**Third**	**Postpartum**
LS (30/15)	A	1.35 ± 0.18[a,b]	1.22 ± 0.15	1.25 ± 0.14	1.30 ± 0.16
	B	1.21 ± 0.11	—	1.26 ± 0.16	—
	C	1.30 ± 0.2			
CT	A	1.27 ± 0.13	1.25 ± 0.08	1.25 ± 0.11	1.32 ± 0.15
	B	1.23 ± 0.07	—	1.21 ± 0.07	—
	C	1.24 ± 0.11			
EI	A	1.38 ± 0.14[c]	1.35 ± 0.12	1.29 ± 0.09	1.38 ± 0.20
	B	1.42 ± 0.12[d]	—	1.32 ± 0.12	—
	C	1.35 ± 0.16			

[a] $P < 0.02$ *versus B.*

[b] $P < 0.04$ *compared to Second A.*

[c] $P < 0.05$ *compared to Third A.*

[d] $P < 0.05$ *compared to Third B.*

in the third trimester as a result either of an intensified subcutaneous insulin-injection program or the use of a continuous insulin-infusion pump. IDDM pregnant women had a higher frequency of cesarean sections, related to a higher frequency of LGA infants. The relationship between glycemic control and the incidence of LGA infants is not clear; controversial data are reported in the literature[28–30] and our results do not support any association.

It is noteworthy that no congenital malformations were found in the children of our diabetic patients, perhaps related to mothers' satisfactory metabolic control during pregnancy.

There is a continuing debate on the effects of pregnancy and of rapid normalization of glycemia on diabetic retinopathy. In agreement with Jovanovic-Peterson and Peterson,[13] our study shows that patients without retinopathy at the beginning remained free from retinal damage during pregnancy. The frequency of retinopathy in our IDDM pregnant women was 56%—lower than that reported by Klein et al.,[14] who found 71% in their 133 patients, with a disease duration comparable to that of our patients (11 ± 7 years). Moloney et al.,[15] reported 62% retinopathy but their sample was more homogeneous (all 53 patients had a disease duration of 10 years).

In our study, retinopathy worsened from mild to moderate nonproliferative during pregnancy only in one patient (16%), but this state regressed to mild after pregnancy. This progression rate was lower than that reported by Kitzmiller et al.,[16] who observed a progression of baseline retinopathy in 43% of their 64 patients—a figure very similar to that of Rodman et al.,[17] who reported a 10% progression in 201 patients during pregnancy and an improvement after delivery. While our data do not allow definite conclusions, due to the limited number of patients and heterogeneity of the sample, consistent with the results of Rodman et al.,[17] they do suggest that pregnancy (1) does not favor the appearance of retinopathy; (2) does not negatively affect mild to moderate nonproliferative retinopathy; and (3) does not induce progression to proliferative retinopathy as described by other authors[18]. The only patient in whom moderate nonproliferative retinopathy progressed to severe showed this change 6 months after delivery, probably related to degree of metabolic control, as she underwent major worsening after delivery (HbA_{1c} from 7.0% to 10.0%).

The average MCV of the peroneal nerve showed a progressive increase during pregnancy in IDDM pregnant women, possibly related to improved metabolic control. The non-significant increase in average SCV may otherwise be attributed to the higher noise associated with the recording of this parameter. As Gregersen,[31] first showed in 1967, normalization of blood glucose in young hyperglycemic diabetic patients at diagnosis can improve or even normalize altered MCVs, and this fact was later confirmed in human and experimental diabetes. Nerve conduction velocity is substantially influenced by physiologic events at the nodes of Ranvier, and their adjustment by good metabolic control may well explain the observed improved behavior. The amplitudes of action potential failed to show any change during the study: however, because this measurement depends on the number of healthy large myelinated fibers, it is unlikely that meaningful structural changes can take place in the time span of a pregnancy.

At baseline, our IDDM pregnant women did not

show any signs of clinical diabetic polyneuropathy, and eight of 16 had slightly reduced nerve conduction velocities. It is reasonable to assume that peripheral nerve involvement was sufficiently functional to be amenable to rapid improvement as a result of good metabolic status.

There are very few data in the literature on peripheral neuropathy in pregnancy. In a prospective study, Nylund et al.,[11] evaluated this complication in 20 IDDM pregnant women with disease durations comparable to those of our patients, but could not find any worsening of motor or sensory conduction velocities during pregnancy. Their control group was composed of nondiabetic nonpregnant women. Our study, which we believe is the first to contain a control group of age-matched nondiabetic pregnant women, supports Nylund's suggestion that pregnancy in itself does not constitute a factor of impairment of nerve conduction velocity.

Cardiovascular reflex function tests were within age-adjusted normal limits in all our patients. None was affected by diabetic autonomic neuropathy, and pregnancy did not have adverse autonomic function effects in diabetic women. It is interesting that pregnancy consistently blunted the response to deep breathing in both diabetic and nondiabetic pregnant women in the third trimester, but this response was temporary, as may be judged by the recovery of response 6 months after delivery in IDDM patients. The reversibility of the DB response and the absence of this effect on the other tests does not suggest a decrease in cardiovagal competence during pregnancy. The reduced response observed in the third trimester was probably due to decreased ventilatory excursion which, obviously, cannot be ''maximal'' because of the pressure of the fetus on the diaphragm.

In conclusion, our study indicates that diabetic women with mild or no retinopathic or neuropathic complications are not adversely affected by pregnancy.

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