Autonomic Influence on Pregnancy Outcome in IDDM

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We evaluated the autonomic influence on pregnancy outcome with prospective study of 100 consecutive pregnancies in women with insulin-dependent diabetes mellitus (IDDM). Tests of cardiovascular autonomic nervous function were performed at the beginning of each pregnancy, and two groups were formed. Group 1 was comprised of 23 pregnancies with autonomic dysfunction, and group 2 was comprised of 77 pregnancies with no abnormalities in cardiovascular tests. Elective abortion was later induced for medical reasons in two cases in group 1, and these women were excluded from the study. The groups were comparable with respect to age, duration of diabetes, and presence of nephropathy. Both groups also achieved comparable glycemic control during pregnancy. There were no significant differences between groups 1 and 2 in any specific pregnancy complication (spontaneous abortions, 5 vs. 3%; perinatal mortality, 10 vs. 1%; congenital malformations, 10 vs. 4%; respiratory distress syndrome, 5 vs. 8%; preeclampsia, 20 vs. 10%; maternal ketoacidosis, 4 vs. 0%; and maternal hypoglycemic accidents, 10 vs. 4%, respectively), but the frequency of pregnancies with at least one of the above complications was greater in group 1 (52 vs. 23%, $P = 0.01$). Stepwise logistic regression analysis showed the association between autonomic dysfunction and pregnancy outcome to be independent of high initial glycosylated hemoglobin levels, long duration of diabetes, and nephropathy. Maternal autonomic dysfunction seems to be associated with an increased frequency of overall pregnancy complications but does not significantly interfere with the achievement of tight metabolic control during pregnancy. *Diabetes Care* **13:756–61, 1990**

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The optimal management of diabetic pregnancy continues to be an important clinical challenge. Poor metabolic control of diabetes before and during pregnancy and the presence of late diabetic complications may jeopardize maternal and fetal well-being (1,2). The potential harmful effects of diabetic autonomic neuropathy are unknown in this respect.

The autonomic nervous system plays an important role in adapting the heart and circulation to various situations, and thus it is possible that autonomic neuropathy may disturb normal cardiovascular adjustments to pregnancy and endanger the outcome. Autonomic neuropathy is also associated with defective glucose counterregulation and hypoglycemia unawareness (3–5). Patients with such disorders are at risk of severe hypoglycemia, especially during intensive insulin therapy. Therefore, the presence of autonomic neuropathy may interfere with the chances of safely achieving strict metabolic control, which is a fundamental therapeutic goal during pregnancy. Thus, we evaluated the effect of autonomic nervous function on the outcome of 100 pregnancies in women with insulin-dependent diabetes mellitus (IDDM) admitted to our hospital.

RESEARCH DESIGN AND METHODS

Our study was comprised of 100 pregnancies in 90 IDDM women admitted to the Department of Obstetrics

during the first trimester of their pregnancies between 1983 and 1987. Their ages ranged from 18 to 40 yr, and duration of diabetes ranged from 0 to 28 yr. Forty-seven patients had retinal changes (39 patients with background retinopathy, 8 patients with proliferative retinopathy) assessed by an ophthalmologist by use of fundoscopy with dilated pupils. Nine patients had diabetic nephropathy, but none had kidney failure. Diabetic nephropathy was diagnosed on the basis of proteinuria >0.5 g/24 h before pregnancy in a diabetic woman without clinical evidence or history of other kidney disease. None had any medication or systemic disease known to affect autonomic nervous function.

Patient management during pregnancy. The patients were admitted to the ward for a few days as soon as the pregnancy was verified (in the 9th wk on average). Only a few of them had been seen at a prepregnancy clinic before pregnancy. A comprehensive evaluation of diabetes control and possible late diabetic complications was carried out along with an obstetric examination. Metabolic control was optimized, and the cooperation of the patient was secured. The optimal goals for blood glucose values were 3.5–5.0 mM before breakfast, 4.0–6.0 mM before meals, 6.5–8.0 mM 2 h after meals, and >3.5 mM from 0200 to 0400. The target glycosylated hemoglobin level, determined by an electrophoretical method (Corning, Halstead, UK), was 8–9%. All the diabetic women monitored their blood glucose at home with a reflectance meter. A 7- to 9-point blood glucose profile was obtained 2–3 days/wk, consisting of measurements made before and 1–2 h after each meal, at 2400, and at 0400. Multiple daily insulin injections were used in 96 pregnancies, and continuous subcutaneous insulin-infusion pumps were used in 4 pregnancies.

After the initial visit, the patients were seen in the ward for 2 days every 4 wk up to 28 wk of pregnancy and every 2 wk thereafter. Between hospital checkups, the patients telephoned a member of our diabetes team once a week to report on their general state of health and blood glucose profiles to allow dynamic adjustments to be made to the treatment. They were usually readmitted to the ward for final close supervision at 37 wk. The timing and method of delivery was determined individually, the objective being to try to carry the pregnancy as near to term as possible (38–40 wk). The infants were examined by a neonatologist at least three times: at birth, at 1 day of age, and on discharge from the hospital. Further diagnostic examinations were carried out when necessary.

Tests of autonomic nervous function. Tests of autonomic nervous function were performed during the first stay in hospital (mean gestational age 9 wk) by specially trained nurses in the cardiovascular laboratory with a method previously described in detail (6). We have shown that early pregnancy does not influence test results (6).

Continuous beat-to-beat heart rate was recorded on a paper strip with a Hewlett-Packard 8812A rate computer (Andover, MA), while the subjects performed six cycles of maximal inspiration and expiration at the rate of 6 breaths/min in a supine position. The difference between the maximum and minimum heart rate during each breath was measured, and the mean was the heart-rate variation in deep breathing. The heart-rate (30:15) and blood pressure responses to standing up were also determined with a standard technique (6). The test records were analyzed without knowing the patient data. The team responsible for the care of the patients was not informed of the results of the tests.

Age-related normal values for heart-rate responses were derived from 63 healthy subjects aged 17–39 yr. Because of the skewness of the distribution of the data, a logarithmic transformation was performed. The mean −2 SD was the lower limit of normal. Thus, a heart-rate variation in deep breathing <15 beats/min in subjects <30 yr old, and <12 beats/min in subjects 30–39 yr old, was considered abnormal; the respective values for the 30:15 ratio were <1.08 and <1.01. Postural hypotension was defined as a drop in systolic blood pressure ≥30 mmHg on standing. The protocol was approved by the local ethics committee, and all the subjects gave their informed consent.

Preeclampsia was diagnosed if blood pressure after the 24th wk of pregnancy was repeatedly ≥140/90 mmHg combined with the occurrence of proteinuria (≥0.3 g/day). In patients with preexisting elevated blood pressure and proteinuria, an increase in blood pressure ≥30/15 mmHg with at least a 100% increase in proteinuria was considered to be preeclampsia. A hypoglycemic accident of the mother was defined as a hypoglycemic symptom necessitating intervention by another person. Respiratory distress syndrome of the newborn was recorded only when it was severe enough to be treated with mechanical ventilation. Milder respiratory disorders treated with supplemental oxygen were classified as minor respiratory disorders. Hypoglycemia of the newborn was defined as a blood glucose level <1.7 mM.

Statistical methods. Comparisons between groups were made by χ^2-test and Fisher's exact test for dichotomous variables. If the variable was continuous, *t* test was used, unless skewness or curtosis of distribution was suspected, in which case the Mann-Whitney *U* test was employed. Analysis of variance (ANOVA) for repeated measures (followed by *t* test) was used for comparison of the groups at multiple time points (Fig. 1). Stepwise logistic regression analysis was used to determine whether the association between autonomic neuropathy and pregnancy complications was independent of other known risk factors. Data are means ± SD.

RESULTS

Abnormal autonomic nervous function tests were found in 22 women at the beginning of 23 pregnancies. Postural hypotension was found in 1 woman, and the rest

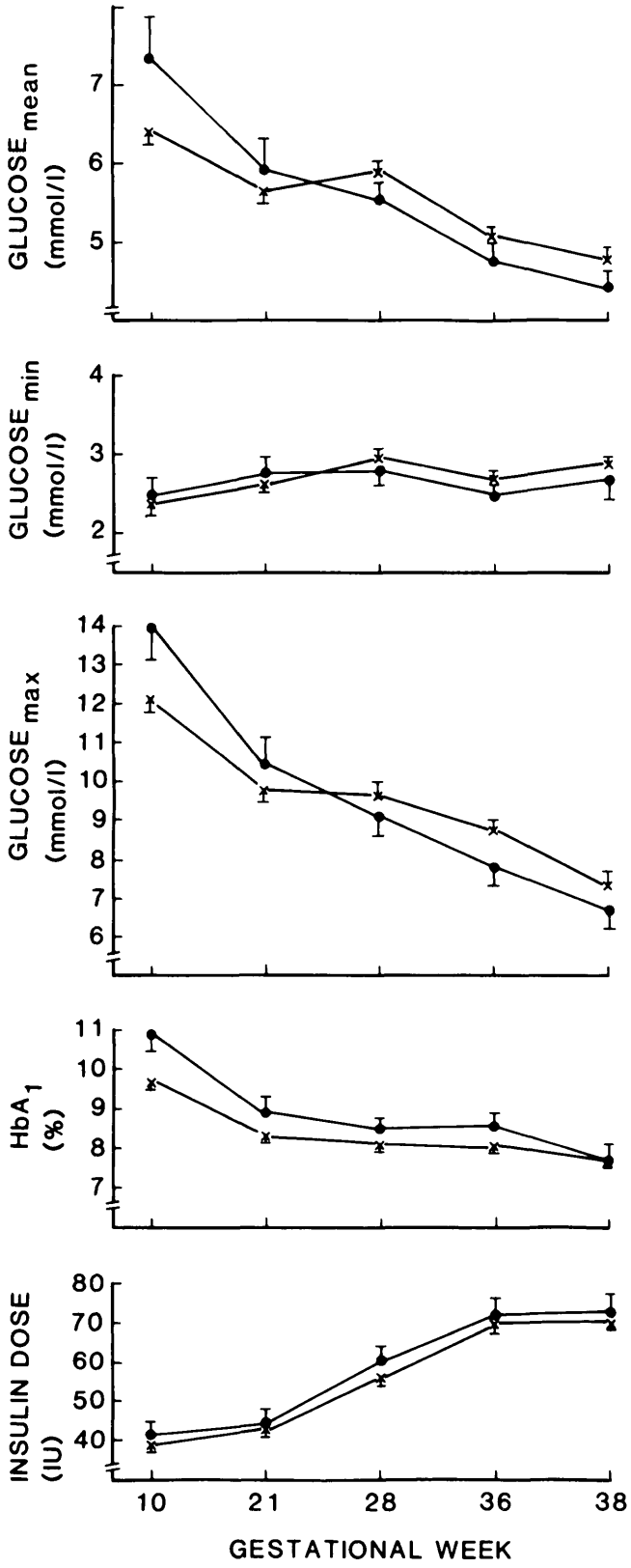

FIG. 1. Mean, minimum, and maximum daily blood glucose concentrations ($glucose_{mean}$, $glucose_{min}$, $glucose_{max}$), HbA_1 concentrations, and daily insulin doses in group 1 (●) and group 2 (×) determined during hospital visits at given week of gestation. Values are means ± SE.

of the abnormalities occurred in heart-rate responses to deep breathing (n = 21) and standing up (n = 8). The pregnancies were divided into two groups on the basis of the test results. Group 1 consisted of 23 pregnancies with at least one abnormal autonomic nervous function test, and group 2 consisted of 77 pregnancies with no such disorders. Two pregnancies in group 1 were later excluded because of elective abortions. In one case, abortion was recommended because of nephropathy and marked visual impairment, and the other was induced on the basis of Fragile X syndrome found in early amniocentesis. The groups did not differ significantly with respect to any other clinical feature except for tests of autonomic nervous function and a slightly higher diastolic blood pressure and increased frequency of White class R in group 1 (Table 1).

Figure 1 shows that at the beginning of the pregnancy,

TABLE 1
Clinical and laboratory data on diabetic women with (group 1) and without (group 2) autonomic dysfunction

	Group 1	Group 2
n	21	77
Age (yr)	25.8 ± 3.8	26.3 ± 4.3
Duration of diabetes (yr)	12.7 ± 5.6	11.6 ± 6.3
Body mass index (kg/m²)	22.9 ± 2.0	22.7 ± 3.1
Heart rate (beats/min)		
Supine	73 ± 12	73 ± 10
Standing	88 ± 15	90 ± 12
Blood pressure (mmHg)		
Supine		
Systolic	119 ± 10	115 ± 10
Diastolic*	74 ± 9	70 ± 8
Standing		
Systolic	113 ± 14	114 ± 12
Diastolic	74 ± 10	74 ± 9
Heart-rate response to hyperventilation (beats/min)†	11.3 ± 5.1	24.9 ± 7.9
30:15†	1.17 ± 0.12	1.39 ± 0.19
Creatinine (μM)	67 ± 9	66 ± 9
Retinopathy	10 (48)	35 (45)
Nephropathy	2 (10)	5 (6)
Smoking	7 (33)	14 (18)
First pregnancy	11 (52)	39 (51)
White classification‡		
B	5 (23)	18 (23)
C	6 (29)	28 (36)
D	5 (23)	25 (32)
R§	3 (14)	1 (1)
F + RF	2 (10)	5 (6)

Values are means ± SD, with percentages in parentheses. 30:15, Ratio of longest R-R interval at ~30th beat after standing to shortest at ~15th beat after standing.

*P = 0.05; †P < 0.001; §P < 0.05.

‡Class B, onset age ≥20 yr, duration of diabetes <10 yr; class C, onset age 10–19 yr or duration of diabetes 10–19 yr; class D, onset age <10 yr or duration of diabetes >20 yr, background retinopathy, or hypertension; class R, proliferative retinopathy or vitreous hemorrhage; class F, nephropathy with >0.5 g/day proteinuria; class RF, coexistence of criteria for R and F.

the mean blood glucose and glycosylated hemoglobin levels were slightly higher in group 1, but the differences did not reach statistical significance ($P = 0.21$ by ANOVA). One woman with abnormal autonomic nervous function had profound ketoacidosis during the 5th wk of pregnancy. Similar good metabolic control was achieved in both groups during pregnancy, and their insulin requirements were comparable (Fig. 1). Hypoglycemic accidents occurred during five pregnancies (5%), including two (10%) in group 1.

There was no maternal mortality. The perinatal mortality rate was 3%, and the frequency of congenital malformations was 5% (Tables 2 and 3). The groups did not differ with respect to the occurrence of any specific pregnancy complication (Table 2), but the overall frequency of pregnancy complications was higher in group 1 ($P = 0.01$; Table 4). In univariate analysis, smoking was also associated with increased frequency of complicated pregnancy ($P = 0.04$), but the association of high initial glycosylated hemoglobin levels ($P = 0.18$), long duration of diabetes ($P = 0.10$), and nephropathy ($P = 0.09$) did not reach statistical significance. Stepwise logistic regression analysis showed the association between autonomic neuropathy and pregnancy complications to be independent of these other risk factors.

TABLE 2
Pregnancy outcome in diabetic women with (group 1) and without (group 2) autonomic dysfunction

	Group 1	Group 2
n	21	77
Gestational age (wk)	36.4 ± 5.1	37.9 ± 3.1
Birth weight (g)	3340 ± 1020	3620 ± 740
Cesarean section	13 (65)	38 (51)
Fetal and neonatal complications		
Spontaneous abortions*	1 (4)	2 (3)
Perinatal mortality	2 (9)	1 (1)
Congenital malformations†	2 (9)	3 (4)
Respiratory distress syndrome	1 (5)	6 (8)
Minor respiratory disorders	6 (32)	17 (22)
Hypoglycemia	6 (33)	17 (22)
Maternal complications		
Premature delivery‡	4 (20)	6 (8)
Preeclampsia	4 (20)	8 (10)
Marked polyhydramnion	1 (4)	1 (1)
Hypoglycemic accidents	2 (10)	3 (4)
Ketoacidosis	1 (4)	0 (0)

Values are means ± SD, with percentages in parentheses.
*Two at 10th wk and 1 at 17th wk.
†One lethal anomaly.
‡Fetuses were <37 gestational wk of age.

DISCUSSION

This study provides prospective data on the course of pregnancy in diabetic women with autonomic dysfunction. It shows that their frequency of pregnancy complications is more than twice that observed in women with no such disorders.

Near normalization of the maternal glucose level throughout the pregnancy is the most crucial factor for preventing fetal problems related to diabetes. Several studies have shown that many patients with autonomic neuropathy have impaired glucose counterregulation to hypoglycemia and diminished hypoglycemia-related warning symptoms (3–5). These features may increase the risk of severe iatrogenic hypoglycemia and interfere with the achievement of strict and safe metabolic control. In this study, the women with autonomic dysfunction tended to have less satisfactory glycemic control at the beginning of the pregnancy, but their later control was similar to that of the women with normal autonomic function. Despite comparable glycemic control during late pregnancy, no significant increase in the frequency of hypoglycemic accidents was observed in the women with autonomic dysfunction. However, the size of the study group is small for reliable evaluation of potential differences in low-frequency complications. Table 3 shows that the initial glycosylated hemoglobin level was high in some of the cases, with congenital malformations in both diabetic groups. Thus, poor glycemic control in early pregnancy may contribute to certain congenital malformations in this series (7,8). However, it must be emphasized that stepwise logistic regression analysis showed that the increase in overall pregnancy complications was independent of poor metabolic control, long duration of disease, and presence of nephropathy.

Achievement of good metabolic control assessed by blood glucose levels does not guarantee that no pregnancy complications will develop or that the fetus will be unaffected. Vascular complications may also increase the risk of congenital malformations and certain maternal complications, e.g., preeclampsia and polyhydramnios (1,2,9–11). The autonomic nervous system

TABLE 3
Data on pregnancies resulting in perinatal mortality or congenital malformation

Patient	Age (yr)	Duration of diabetes (yr)	White class*	HbA_1 (%)	Group	Complication
1†	28	3	B	7.9	1	Stillbirth at 24 wk
2†	24	3	B	9.7	2	Stillbirth at 37 wk
3	22	19	D	10.7	1	Lethal aortic atresia
4	24	10	C	13.7	2	Tetralogy of Fallot
5	23	22	F	13.3	2	Atrial and ventricular septal defects
6	21	18	D	14.9	1	Vertebral anomaly
7	30	18	D	10.7	2	Hydrocele testis

*Class B, onset age ≥20 yr, duration of diabetes <10 yr; class C, onset age 10–19 yr or duration of diabetes 10–19 yr; class D, onset age <10 yr or duration of diabetes >20 yr, background retinopathy, or hypertension; class F, nephropathy with >0.5 g/day proteinuria.
†No specific cause of death at autopsy.

TABLE 4
Overall frequency of complicated pregnancies according to presence of autonomic dysfunction, microvascular complications, and White classification

		Autonomic dysfunction		
	n	Yes (*n* = 21)	No (*n* = 77)	*P*
Nephropathy	7	1 (50)	3 (60)	0.71
Retinopathy, no nephropathy	38	5 (63)	5 (17)	0.03
No microvascular complications	53	5 (45)	10 (24)	0.30
White classes*				
B, C, D	87	7 (44)	15 (21)	0.06
R, F, RF	11	4 (80)	3 (50)	0.55
Total		11 (52)	18 (23)	0.01

Values in parentheses are percentages. All pregnancies had at least one of the following complications: spontaneous abortion, perinatal mortality, malformation, respiratory distress syndrome of newborn and preeclampsia, ketoacidosis, or hypoglycemic accidents of the mother. *Class B, onset age ≥20 yr, duration of diabetes <10 yr; class C, onset age 10–19 yr or duration of diabetes 10–19 yr; class D, onset age <10 yr or duration of diabetes >20 yr, background retinopathy, or hypertension; class R, proliferative retinopathy or vitreous hemorrhage; class F, nephropathy with >0.5 g/day proteinuria; class RF, coexistence of criteria for R and F.

plays a fundamental role in adapting the heart and circulation to varying peripheral demands, presumably also during pregnancy. Our previous studies (based on a subgroup of these diabetic women) have shown that the cardiovascular adjustments to pregnancy are impaired in diabetic women (6,12). Diabetic autonomic neuropathy and preclinical changes in left ventricular function, which are often found in young diabetic women (13), may contribute to these impaired adjustments. Diabetic autonomic neuropathy also seems to be associated with an abnormal left ventricular filling pattern and abnormal cardiovascular response to exercise (14–16). These reduced cardiac reserves may endanger fetal well-being through impaired uteroplacental blood flow (17,18).

In accordance with previous reports (2,9–11), pregnancy complications were common in women with nephropathy and/or proliferative retinopathy (Table 4). On the other hand, autonomic dysfunction with no coexistent microvascular complications was also associated with a comparable high frequency of pregnancy complications (Table 4).

These findings support the view that the hemodynamic and metabolic abnormalities associated with diabetic autonomic neuropathy are clinically important during pregnancy. Furthermore, it must be emphasized that most of the women with autonomic dysfunction had only mild asymptomatic abnormalities in parasympathetic function. It is possible that more profound abnormalities may be of even greater prognostic importance. Because autonomic neuropathy is a common abnormality in young asymptomatic diabetic women, screening for this disorder may be advisable before conception or early in the pregnancy, because pregnancy itself and its possible complications later modify the autonomic nervous function tests and make testing unreliable (6,19,20).

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REFERENCES

1. Hare JW, White P: Pregnancy in diabetes complicated by vascular disease. *Diabetes* 26:953–55, 1977
2. Miodovnik M, Mimouni F, Dignan PStJ, Berk MA, Ballard JL, Siddiqi TA, Khoury J, Tsang RC: Major malformations in infants of IDDM women: vasculopathy and early first-trimester poor glycemic control. *Diabetes Care* 11:713–18, 1988
3. Hoeldke RD, Boden G, Shuman CR, Owen OE: Reduced epinephrine secretion and hypoglycemia unawareness in diabetic autonomic neuropathy. *Ann Intern Med* 96:459–62, 1982
4. Hilsted J, Madsbad S, Krarup T, Sestoft L, Christensen NJ, Tronier B, Galbo H: Hormonal, metabolic, and cardiovascular responses to hypoglycemia in diabetic autonomic neuropathy. *Diabetes* 30:626–33, 1981
5. Cryer PE, Gerich JE: Glucose counterregulation, hypoglycemia and intensive insulin therapy in diabetes mellitus. *N Engl J Med* 313:232–41, 1985
6. Airaksinen KEJ, Salmela PI, Ikäheimo MJ, Kirkinen P, Linnaluoto MK, Takkunen JT: Effect of pregnancy on autonomic nervous function and heart rate in diabetic and nondiabetic women. *Diabetes Care* 10:748–51, 1987
7. Miller E, Hare JW, Cloherty JP, Dunn PJ, Gleason RE, Soeldner JS, Kitzmiller JL: Elevated maternal hemoglobin A_{1c} in early pregnancy and major congenital anomalies in infants of diabetic mothers. *N Engl J Med* 304:1331–34, 1981
8. Mills JL, Knopp RH, Simpson JL, Jovanovic-Peterson L, Metzger BE, Holmes LB, Aarons JH, Brown Z, Reed GF, Bieber FR, van Allen M, Holzman I, Ober C, Peterson CM, Withiam MJ, Duckles A, Mueller-Heubach E, Polk BF, and the National Institute of Child Health and Human Development Diabetes in Early Pregnancy Study: Lack of relation of increased malformation rates in infants of diabetic mothers to glycemic control during organogenesis. *N Engl J Med* 318:671–76, 1988
9. Kitzmiller JL, Brown ER, Phillippe M, Stark AR, Acker D, Kaldany A, Singh S, Hare JW: Diabetic nephropathy and perinatal outcome. *Am J Obstet Gynecol* 141:741–51, 1981
10. Molsted-Pedersen L, Tygstrup I, Pedersen J: Congenital malformations in newborn infants of diabetic women:

correlation with maternal diabetic vascular complications. *Lancet* 1:1124–26, 1964
11. Price JH, Hadden DR, Archer DB, Harley JMcDG: Diabetic retinopathy in pregnancy. *Br J Obstet Gynaecol* 91:11–17, 1984
12. Airaksinen KEJ, Ikäheimo MJ, Salmela PI, Kirkinen P, Linnaluoto MK, Takkunen JT: Impaired cardiac adjustment to pregnancy in type I diabetes. *Diabetes Care* 9:376–83, 1986
13. Airaksinen J, Ikäheimo M, Kaila J, Linnaluoto M, Takkunen J: Impaired left ventricular filling in young female diabetics: an echocardiographic study. *Acta Med Scand* 216:509–16, 1984
14. Hilsted J, Galbo H, Christensen NJ: Impaired cardiovascular responses to graded exercise in diabetic autonomic neuropathy. *Diabetes* 28:313–19, 1979
15. Zola B, Kahn JK, Juni JE, Vinik AI: Abnormal cardiac function in diabetic patients with autonomic neuropathy in the absence of ischemic heart disease. *J Clin Endocrinol Metab* 63:208–14, 1986
16. Airaksinen KEJ, Koistinen MJ, Ikäheimo MJ, Huikuri HV, Korhonen U, Pirttiaho H, Linnaluoto MK, Takkunen JT: Augmentation of atrial contribution to left ventricular filling in IDDM subjects as assessed by Doppler echocardiography. *Diabetes Care* 12:159–61, 1989
17. Ahokas RA, Anderson GD, Lipshitz J: Cardiac output and uteroplacental blood flow in diet-restricted and diet-repleted pregnant rats. *Am J Obstet Gynecol* 146:6–13, 1983
18. Nylund L, Lunell N-O, Lewander R, Person B, Sarby B: Uteroplacental blood flow in diabetic pregnancy: measurements with indium 113m and a computer-linked gamma camera. *Am J Obstet Gynecol* 144:292–302, 1982
19. Souma ML, Cabaniss CD: The Valsalva maneuver: a test of autonomic nervous system function in pregnancy. *Am J Obstet Gynecol* 145:274–78, 1983
20. Airaksinen KEJ, Kirkinen P, Takkunen JT: Autonomic nervous dysfunction in severe pre-eclampsia. *Eur J Obstet Gynecol Reprod Biol* 19:269–76, 1985