Congenital Malformations in Pregnancies Complicated by NIDDM

Increased risk from poor maternal metabolic control but not from exposure to sulfonylurea drugs

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OBJECTIVE — To determine whether the use of oral hypoglycemic agents during early pregnancy is associated with a risk of congenital malformations in infants of mothers with non-insulin-dependent diabetes mellitus (NIDDM) independent of maternal metabolic control.

RESEARCH DESIGN AND METHODS — From a prospectively collected database of pregnancies complicated by diabetes at a large urban medical center, we identified 332 consecutive infants born to women with NIDDM who did not participate in a preconceptional diabetes care program. Stepwise logistical regression was used to identify maternal characteristics that were independently associated with risks of major and minor congenital malformations in infants.

RESULTS — Overall, 56 (16.9%) of the 332 infants were born with congenital anomalies (11.7% major anomalies and 5.1% minor anomalies). Analysis of data from subgroups of women who were treated with diet therapy, exogenous insulin, or sulfonylurea compounds during the first 8 weeks of gestation did not reveal statistically significant differences in major or minor malformation rates among the three groups. Stepwise logistic regression analysis revealed two maternal characteristics that were independently associated with major malformations in infants: maternal HbA_{1c} at initial presentation for care (direct relationship; $P = 0.0007$) and the maternal age at onset of diabetes (inverse relationship; $P = 0.009$). The risk of major malformations was unrelated to the mode of antidiabetic therapy during early pregnancy. No relationship was found between maternal glycemia or treatment modality and rates of minor congenital anomalies.

CONCLUSIONS — These data indicate that, in the absence of special preconceptional care, NIDDM is associated with a risk for major congenital anomalies that is in the range reported for pregnancies complicated by insulin-dependent diabetes mellitus. Moreover, the risk in individual patients appears to be related to maternal glycemic control rather than to the mode of antidiabetic therapy during early pregnancy.

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IDDM, insulin-dependent diabetes mellitus; NIDDM, non-insulin-dependent diabetes mellitus; OHA, oral hypoglycemic agents.

Maternal diabetes is known to increase the risk of major congenital malformations in infants (1–12). To date, most reports of malformation rates in offspring of mothers with diabetes either have not specified the type of maternal diabetes (1–6) or have focused on mothers with insulin-dependent diabetes mellitus (IDDM) (7,8). The few studies that have reported malformation rates in offspring of women with non-insulin-dependent diabetes mellitus (NIDDM) (10,11,13,14) were very small and/or were not designed to distinguish between possible teratogenic effects of poor maternal metabolic control and fetal exposure to oral hypoglycemic agents (OHAs) during early pregnancy. The present study was conducted to determine the malformation rates in offspring of a large group of women with NIDDM and to determine the relative impact of maternal glycemic control and the modality of maternal antidiabetic therapy during early pregnancy on the risk of malformations in infants.

RESEARCH DESIGN AND METHODS

— Beginning on 1 January 1987, clinical data from all pregnancies complicated by diabetes at the Los Angeles County + University of Southern California Women's Hospital were collected prospectively and entered into a computerized database for analysis. The database includes the following: information on the maternal obstetrical history; age at onset, type of therapy, and complications of maternal diabetes; gestational age and type of metabolic management at the time of presentation for antepartum care; medication, alcohol, and tobacco use during pregnancy; and fetal outcome. Liveborn infants of mothers with diabetes are admitted to a neonatal observation unit where they have a detailed physical examination, including an examination for anomalies by faculty neonatologists and geneticists. Findings that suggest an anomaly are confirmed by additional testing as clinically indicated (e.g., cardiac imaging for suspected cardiac anomalies).

Stillborn infants have autopsies or a detailed physical examination if an autopsy is refused.

For the present report, all women whose pregnancies were complicated by pregestational NIDDM and whose infants were delivered by 31 December 1993 were identified from the database on the basis of a clinical history of diabetes that had been managed for at least 6 months after diagnosis without exogenous insulin therapy. Patients with a history of diabetic ketoacidosis were excluded from the analysis. Women who were using insulin when they came for their initial antepartum care were included in the analysis if they gave a history of management without insulin after their initial diagnosis.

Patients were assigned to three study groups according to the form of antidiabetic therapy that they had used during the first 8 weeks of gestation: *1*) diet therapy alone, 2) diet therapy plus OHAs, and 3) diet therapy plus exogenous insulin. Women who reported OHA use during any part of the first 8 weeks of gestation were included in the OHA group for data analysis. Some of those women had stopped using the medication by the time of their initial antepartum visit, but none of them had been placed on insulin therapy before that visit. Women who participated in a preconceptional diabetes care program and who had pregnancies that ended in spontaneous abortion before 20 weeks of gestation were excluded from the analysis. Stillbirths and elective abortions that were performed for anomalies diagnosed in utero were included in the analysis.

Congenital anomalies were classified as major or minor and as single or multiple. Major anomalies were lethal, caused significant morbidity, or required surgical repair; all other anomalies were considered minor. The major anomalies were further classified into two categories: anomalies not known to be associated with a specific genetic defect and anomalies resulting from known genetic syndromes. Infants with multiple anomalies were counted only once in the determination of the overall malformation rates, and they were classified in the category of major anomalies if both major and minor anomalies were present. Specific types of anomalies were tabulated on the basis of the organ system(s) involved: central nervous system, face, heart and great vessels, gastrointestinal tract, genitourinary tract, and skeleton (including the caudal regression syndrome). For this tabulation, each malformation was counted once, allowing one infant to be included more than once if multiple organ systems were malformed.

Glucose in serum from individuals who fasted overnight was measured by a glucose oxidase method (Beckman Glucose Analyzer II, Beckman, Brea, CA). HbA_{1c} was measured by boronate affinity ion-exchange chromatography (Glycoglobin Kit, Endocrine Sciences, Tarzana, CA). The normal range for HbA_{1c} determined by this method (i.e., the mean ± 2 SD for individuals without diabetes) was 4.9–7.5%.

The statistical significance of differences among treatment groups was assessed by analysis of variance for continuous variables and by χ^2 analysis for categorical variables. Logistic regression analysis was used to test whether individual maternal characteristics that differed among groups with major, minor, and no anomalies or among treatment groups were associated with the risk of malformations in offspring. Stepwise logistic regression analysis was used to identify maternal characteristics that were independently associated with the risk of malformations. Each infant was considered separately for these regression analyses. Data are presented as means ± SE.

Table 1—*Rates of major and minor congenital anomalies by organ system in 332 offspring of mothers with pregestational NIDDM*

Organ system	Major anomalies	Minor anomalies
Central nervous system	7 (2.1)	0
Face	10 (3.0)	10 (3.0)
Heart + great vessels	17 (5.1)	3 (0.9)
Gastrointestinal	3 (0.9)	4 (1.2)
Genitourinary	10 (3.0)	5 (1.5)
Skeletal	8 (2.4)	2 (0.6)
Other	0	7 (2.1)

Data are *n* (%). Major anomalies were lethal, caused significant morbidity, or required surgical repair. Minor anomalies were not classified as major. Other organ systems include sacral skin tags, cutis aplasia of scalp, and hydroceles.

RESULTS — During the 6-year study period, 303 women met the entry criteria for pregnancies complicated by pregestational NIDDM. One woman gave birth to a baby with Down's syndrome; that pregnancy was excluded from the data analysis. The remaining 302 women gave birth to a total of 332 infants (5 women delivered twins, and 16 women had 2 or 3 separate singleton pregnancies during the study period). The women were predominantly Latino and, consistent with the diagnosis of NIDDM, they tended to be overweight (body mass index 29 ± 1 kg/m^2 before conception), to have developed diabetes as adults (age at onset 28 ± 1 years; only 15 patients were <18 years of age at onset), and to have a family history of diabetes in first-degree (50% of patients) and second-degree (22% of patients) relatives.

Overall, 56 (16.9%) of the 332 infants manifested one or more congenital anomaly. Seventeen (5.1%) of the infants manifested only minor anomalies, and 39 (11.7%) manifested major anomalies. Of the malformed infants, 20 (36%) had multiple congenital anomalies, and 10 of those infants had two or more major anomalies. The organ systems that were affected by the anomalies appear in Table 1.

Women who gave birth to infants with major congenital anomalies were significantly younger, had a younger age at onset of diabetes, and had higher fasting glucose and glycohemoglobin concentrations at their initial presentation compared with women who gave birth to normal infants or to infants with only minor anomalies (Table 2). Maternal parity;

Table 2—*Maternal characteristics according to malformation status of offspring in pregnancies complicated by pregestational NIDDM*

Maternal characteristic	Congenital malformations			*P* value
	None	Minor	Major	
n	277	17	38	
Age (years)	32 ± 1	33 ± 2	29 ± 2	<0.004
Parity	2.4 ± 0.1	2.3 ± 0.5	2.1 ± 0.3	NS
Age at onset of NIDDM (years)	28 ± 1	30 ± 1	25 ± 1	<0.004
Duration of NIDDM (years)	3.7 ± 0.2	2.9 ± 0.7	3.8 ± 0.5	NS
Gestational age at initial visit (weeks)	14.2 ± 0.5	13.9 ± 1.8	15.8 ± 1.3	NS
Medication use (%)	8.0	6.3	7.7	NS
Alcohol, tobacco, or drug use (%)	3.7	12.5	0	NS
Initial HbA_{1c} (%)	8.1 ± 0.1	7.7 ± 0.4	9.5 ± 0.4	<0.001
Initial serum glucose (mol/l)	8.8 ± 0.2	9.0 ± 0.7	10.3 ± 0.5	<0.02

Data are means ± SE. Major and minor anomalies are defined in Table 1. *P* values were calculated by analysis of variance for continuous variables and χ^2 analysis for categorical variables. Medication use and alcohol, tobacco, or drug use show the proportion of patients who reported use during the first 8 weeks of pregnancy. Drugs denotes illicit drugs; medications excludes insulin and OHAs. Initial serum glucose was measured at the first prenatal visit; blood was collected after an overnight fast.

duration of diabetes; gestational age at initial presentation; use of medications other than sulfonylureas and insulin; and use of alcohol, tobacco, or illicit drugs did not differ significantly among women whose infants had major, minor, or no anomalies (Table 2).

Of the 332 infants, 125 were born to women who used only diet therapy during the first 8 weeks of gestation, 60 were born to women who used only exogenous insulin, and 147 were born to women who used OHAs for at least part of the first 8 weeks of pregnancy. All of the women who used OHAs reported taking sulfonylurea preparations—predominantly chlorpropamide, glyburide, and glipizide. There were no statistically significant differences among the diet, insulin, and OHA treatment groups regarding maternal age; parity; use of medications other than OHAs or insulin during the first trimester; use of alcohol, tobacco, or illicit drugs; or maternal glycemia (fasting serum glucose or HbA_{1c}) at the initial presentation (Table 3). The women in the insulin-treated group had a significantly younger age at onset of diabetes and a significantly longer duration of diabetes compared with the other two treatment groups. Women in the diet-only group presented for care an average of 3 weeks later than the groups who were using insulin or OHAs at presentation. Rates of minor and major congenital anomalies did not differ significantly among the three treatment groups (Table 3).

Univariate logistic regression analysis using data from all 332 infants revealed four maternal characteristics that were associated with the risk of congenital malformations in offspring (Table 4): the fasting serum glucose concentration and HbA_{1c} concentration at the first antepartum visit, the maternal age during the index pregnancy, and the maternal age at onset of diabetes. Stepwise regression analysis performed on the same data revealed that only the initial maternal HbA_{1c} concentration (higher concentration = greater risk) and the age at onset of diabetes (younger age = greater risk) were independently associated with the risk of malformations in infants. When the univariate and stepwise regression analyses were repeated in the subset of 172 patients who were seen for care during the first 14 weeks of gestation, only measures of maternal glycemia were related to the risk of malformations, and only the HbA_{1c} was independently related to that risk. Thus, maternal glucose control, but not the mode of antidiabetic therapy during early pregnancy, imparted a large portion of the risk for major malformations in infants of mothers with pre-

Table 3—*Maternal characteristics according to antidiabetic treatment during the first 8 weeks of pregnancy*

Maternal characteristic	Antidiabetic treatment			*P* value
	Diet	OHA	Insulin	
n	125	147	60	
Age (years)	32 ± 1	32 ± 1	30 ± 1	NS
Parity	2.4 ± 0.3	2.5 ± 0.3	2.2 ± 0.4	NS
Age at onset of NIDDM (years)	28 ± 1	30 ± 1	25 ± 1	<0.001
Duration of NIDDM (years)	3.6 ± 0.3	3.3 ± 0.2	4.7 ± 0.4	<0.02
Gestational age at initial visit (weeks)	16.2 ± 1.3	13.4 ± 1.5	13.1 ± 1.8	<0.002
Medication use (%)	6.3	9.5	8.5	NS
Alcohol, tobacco, or drug use (%)	3.2	3.4	5.1	NS
Initial HbA_{1c} (%)	8.3 ± 0.2	8.2 ± 0.2	8.1 ± 0.3	NS
Initial serum glucose (mmol/l)	9.2 ± 0.2	8.9 ± 0.2	8.4 ± 0.3	NS
Infants with anomalies (%)				
Major	14.4	9.5	11.7	NS
Minor	4.8	6.1	3.3	NS

Major and minor anomalies are defined in Table 1. Maternal characteristics are defined in Table 2. OHAs were predominantly chlorpropamide, glyburide, and glipizide. *P* values were calculated by analysis of variance for continuous variables and χ^2 analysis for categorical variables.

Table 4—*Results of logistic regression analysis of rates of major malformations in offspring on maternal characteristics in pregnancies complicated by pregestational NIDDM*

Maternal characteristic	All pregnancies			Women presenting at <14 weeks gestation		
	Relative risk	95% confidence interval	*P* value	Relative risk	95% confidence interval	*P* value
Univariate regression						
HbA_{1c} (%)	1.34	1.15–1.56	0.0002	1.42	1.14–1.76	0.0014
Glucose (mol/l)	1.20	1.07–1.34	0.0014	1.24	1.04–1.46	0.014
Age (years)	0.91	0.85–0.96	0.0007	0.94	0.86–1.04	0.23
Onset of NIDDM (years)	0.91	0.86–0.96	0.0012	0.94	0.86–1.03	0.17
Treatment group						
Diet	1.00	—	—	1.00	—	—
OHA	0.64	0.30–1.32	0.22	0.42	0.13–1.42	0.16
Insulin	0.78	0.31–2.00	0.61	0.65	0.16–2.71	0.55
Years of NIDDM	1.01	0.91–1.13	0.79	1.05	0.89–1.24	0.55
Entered care (weeks)	1.03	0.99–1.08	0.18	1.03	0.84–1.26	0.77
Medication use	0.97	0.28–3.40	0.96	0.79	0.09–6.41	0.82
Multivariate regression						
HbA_{1c} (%)	1.31	1.12–1.53	0.0007	1.42	1.14–1.76	0.0014
Onset of NIDDM (years)	0.92	0.87–0.98	0.009	—	—	—

Analyses were done using characteristics that differed among malformation groups or treatment groups (Tables 2 and 3); $n = 332$ for all pregnancies; $n = 172$ for women who presented for care at <14 weeks gestation. For univariate regression, relative risks are for each unit increase in independent variable. Onset of NIDDM shows maternal age at diagnosis of NIDDM. OHAs used were predominantly chlorpropamide, glyburide, and glipizide. Entered care shows gestational age at first prenatal visit. Medication use shows use of nonprescription or prescription medications other than insulin or an OHA. For multivariate regression, relative risks and *P* values adjusted for other independent variable.

gestational NIDDM. None of the maternal factors that we evaluated was associated with a risk of minor congenital anomalies in infants.

Examination of the distribution of maternal glycohemoglobin concentrations and major malformations in the entire study cohort (Fig. 1) revealed that 41% of subjects had HbA_{1c} concentrations in the normal range; 5.8% of their infants had major congenital anomalies. The anomaly rate increased in a progressive fashion with higher HbA_{1c} concentrations (Fig. 1).

CONCLUSIONS— There are three major findings of this study. First, we found that 11.7% of women with NIDDM who did not participate in a preconception care program gave birth to infants with major congenital anomalies. Because our study design did not include an ascertainment of malformation rates in offspring of women without diabetes, we cannot determine with certainty whether maternal NIDDM increased the risk of major malformations in infants born to our patients. However, the 11.7% rate of major malformations is much higher than the <2% rate observed at our hospital in infants born to women who were not known to have diabetes during the period of this study, supporting the concept (10–13,15) that maternal NIDDM imparts an increased risk of major congenital anomalies in infants. Furthermore, the incidence rates of major malformations in the present study and in the study of Pierce et al. (15) are similar to incidence rates reported in many studies (1–8) for major anomalies in infants born to women with IDDM in the absence of special preconceptional care. Thus, those two genetically distinct forms of diabetes appear to impart similar risks of major congenital malformations to infants, possibly through similar metabolic aberrations.

The second major finding of the present study consisted of independent associations between the risk of major malformations in infants and two maternal characteristics: glycemic control in early pregnancy, as assessed by second trimester glycohemoglobin concentrations, and the maternal age at the onset of diabetes. We have no ready explanation for the latter association, which was relatively minor in magnitude. We can conclude that the relationship could not have resulted from the presence of clinically apparent diabetic microangiopathy in patients with an early age at onset because only one patient in the study cohort had

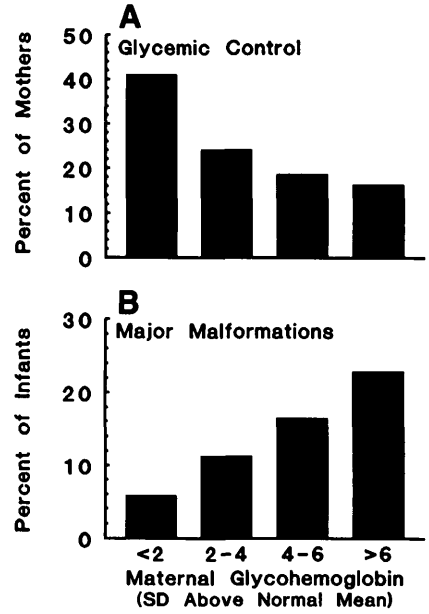

Figure 1—*Distribution of maternal glycohemoglobin (hemoglobin A_{1c}) concentrations (A) and major malformation rates (B) in pregnancies complicated by pregestational NIDDM. Glycohemoglobin concentrations are expressed relative to the normal range (means ± 2 SD) of nondiabetic individuals. Numbers of pregnancies represented in the four glycohemoglobin categories are as follows: <2 SD = 136, 2–4 SD = 80, 4–6 SD = 62, and >6 SD = 54.*

evidence for retinopathy or proteinuria during the first half of gestation. The association between measures of maternal glycemic control and the risk of major malformations is consistent with results of animal studies (16–19) and clinical studies in pregnancies complicated by IDDM (4,20,21) that link exposure to hyperglycemia during embryogenesis to congenital malformations in offspring. The shape of the relationship between maternal glycohemoglobin and the risk of major malformations appeared to be linear in our patient population (Fig. 1). This finding contrasts with some reports from pregnancies complicated by IDDM (4,20) in which a marked increase in malformation rates occurred in offspring of women with very high glycohemoglobin concentrations (i.e., >12 SD above the population mean [20]). The relatively narrow range of glycohemoglobin concentrations in the present study may account for the linear pattern that we observed. The 5.8% rate of malformations in infants of women with initial glycohemoglobin concentrations <2 SD above the normal mean was somewhat surprising, but that finding is consistent with the report of Mills et al. (7) in which women with IDDM and first trimester glycohemoglobin concentrations <2 SD above the normal mean had significantly more malformed infants than nondiabetic women. We did not find any evidence for a relationship between maternal glycemia and the risk of minor malformations in our patients.

The third and most important finding of the present study was the lack of any association between congenital anomalies and the use of OHAs during organogenesis. Rates of major anomalies were lowest in the patients who used OHAs during early pregnancy. More important, use of OHAs was not identified as a risk factor for major anomalies in the univariate or stepwise regression analyses. Thus, the appearance of major malformations in previous reports of women who used OHAs during early pregnancy (13,22–24) may have been related to poor maternal metabolic regulation rather than to an embryotoxic effect of the OHAs per se. We also found no evidence for an association between sulfonylurea use in early pregnancy and minor malformations, including ear anomalies that were reported by Piacquadio et al. (13) in 25% of a small group of infants born to women with NIDDM who took sulfonylurea drugs during pregnancy. Only 10 infants in our cohort had ear anomalies, and only 6 of those were born to women who took sulfonylurea agents. Thus, neither our observations in Hispanic patients nor the findings of Hellmuth et al. (14) in northern European and Oriental women support a role for sulfonylurea drugs in the genesis of malformations in infants of women with NIDDM.

In summary, we found that 11.7% of a large group of Latino women with NIDDM who did not participate in a preconceptional diabetes care program gave birth to infants with major congenital malformations. The rate and types of malformations were similar to the rates and types that have been reported in offspring of women with IDDM. The risk of malformations increased in association with maternal glycohemoglobin concentrations early in the second trimester, which were found to be independently associated with the risk of major, but not minor, malformations in infants. No association was identified between the risk of major or minor malformations in infants and maternal use of sulfonylurea drugs during the first 8 weeks of gestation. Our findings support a role for poor maternal metabolic control, but not for ingestion of sulfonylurea drugs, in the genesis of major congenital malformations in pregnancies complicated by maternal NIDDM. Thus, the focus of counseling for women with NIDDM who become pregnant while taking one of the sulfonylurea compounds reported herein should be on maternal metabolic control rather than on the hypoglycemic agent per se. Whether oral hypoglycemic drugs can be used prospectively to achieve good metabolic control and reduce the risk of congenital malformations in offspring of women with NIDDM remains to be determined.

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