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College of Public Health

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520-429-2746
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Gestational Diabetes Is a Herald of NIDDM in Navajo Women

High rate of abnormal glucose tolerance after GDM

JONATHAN R. STEINHART, MD
JONATHAN R. SUGARMAN, MD
FRED A. CONNELL, MD

OBJECTIVE — To estimate the rate of deterioration of glucose tolerance and evaluate risk factors for development of NIDDM in Navajo women with a history of gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS — A retrospective analysis of 111 GDM deliveries over a 4-year period, 1983–1987, was conducted in 1994 to determine glucose tolerance status. Patients who had not developed NIDDM were recalled for a 2-h glucose tolerance test (GTT). Tested and non-tested patients were compared, an estimate of conversion to NIDDM was calculated, and risk factors for NIDDM were evaluated. A life-table analysis was developed to estimate the probability of NIDDM after GDM.

RESULTS — At the time of chart review, 32 patients (29%) had already been diagnosed with NIDDM. Of the patients, 79 were offered GTT testing, and 56 (71%) returned for follow-up; 15 were diagnosed with NIDDM and 17 with impaired glucose tolerance (IGT); 47 (42%) and 64 (58%) patients in the cohort had developed NIDDM or NIDDM/IGT at the conclusion of the study period. Patients who developed NIDDM had greater BMIs, parity, and infant weights. Fasting blood glucose >5.83 mmol/l, GTT >41.63 mmol/l, and recurrence of GDM were associated with later NIDDM. A life-table analysis estimated a 53% likelihood of having NIDDM at an 11-year follow-up; a second model, based only on patients with known NIDDM status, predicted a 70% rate of NIDDM at an 11-year follow-up.

CONCLUSIONS — A high proportion of Navajo women with GDM progressed to NIDDM. Postpartum counseling and periodic GTTs are recommended.

Gestational diabetes mellitus (GDM) is defined as "carbohydrate intolerance of variable severity with onset or first recognition during pregnancy" (1). Many studies have confirmed the predictive value of GDM for the onset of non-insulin-dependent diabetes mellitus (NIDDM) (2–10). The natural history of impaired glucose tolerance following a pregnancy complicated by GDM varies widely (3). Conversion rates to NIDDM, approximately 6 years following a GDM pregnancy, have been reported to be as low as 13% (3) or as high as 62% (6).

NIDDM in the Native American community was rare before World War II. Today its prevalence in many tribes is greater than that of the general population. Rates vary among tribes: they are highest in the Plains and Pueblo tribes and lowest in the Alaskan Eskimo and Athapaskan tribes such as the Navajo (11,12).

Certain characteristics appear to be risk factors for development of NIDDM following GDM. These characteristics include diagnosis of GDM before age 25, obesity (BMI >29.0), insulin treatment in pregnancy, recurrence of GDM, and increased fasting glucose on the glucose tolerance test (GTT) (5,8,9,13). Parity has not been consistently identified as a risk factor (14).

Higher rates of recurrence of GDM have been associated with increasing severity of glucose intolerance, as measured by the sum of the individual glucose values from the initial GTT exceeding 41.6 mmol/l (15). This relationship has not been evaluated for the later occurrence of NIDDM.

The purpose of this study was *1*) to assess the subsequent development of NIDDM in Navajo women who had been previously diagnosed with GDM, and 2) to evaluate characteristics in the index pregnancy for their predictive value for development of NIDDM.

RESEARCH DESIGN AND METHODS

— Subjects were selected from women who received prenatal care at Shiprock Hospital from 1 October 1983 to 30 September 1987. Shiprock Hospital, located in northwest New Mexico and staffed by the Indian Health Service (IHS), is the principal inpatient facility for approximately 40,000 Navajos who reside in the Four Corners region of the Reservation. Prenatal and postpartum care for patients are provided by a clinic adjacent to the hospital and in other clinics in the Four Corners area.

Universal screening for GDM was initiated in the fall of 1983. All patients were screened for GDM using a 50-g 1-h oral glucose load at their first visit. From 1 October 1983 to 1 May 1986 this screen was repeated at 28–34 weeks for high-risk patients (16). Subsequently, all patients were screened at both their first visit and at 28–32 weeks. In the first 3 years of the study, patients whose screen was ≥7.2 mmol/l (raised to 7.8 mmol/l during the last 14 months of the study period) received a 100-g 3-h oral GTT and were classified as GDM according to accepted American College of Obstetrics and Gynecology guidelines (17). The overall incidence of GDM during the study period was 4.6% (16).

During the study period, 3,988 patients delivered at the hospital. Using

From the Northern Navajo Medical Center (J.R.St.), Public Health Service Indian Hospital, Shiprock, New Mexico; and the School of Public Health and Community Medicine (J.R.Su., F.A.C.), University of Washington, Seattle, Washington.

Address correspondence and reprint requests to Jonathan R. Steinhart, MD, Northern Navajo Medical Center, Box 160, Shiprock, NM 87420. E-mail: jsteinh532@aol.com.

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GDM, gestational diabetes mellitus; GTT, glucose tolerance test; IGT, impaired glucose tolerance.

Table 1—*Selected characteristics of Navajo women with GDM, Shiprock Hospital, 1983–1987*

Variable	
n	111
Age at delivery (years)	31.4 ± 5.7
Age at follow-up (years)	39.3 ± 5.7
Prenatal GTT total (mmol/l)	36.4 ± 4.6
Parity	2.9 ± 2.1
BMI at GTT (kg/m²)	31.6 ± 5.51
Infant weight (g)	3,569 ± 647
Infant weight >4,000 g (%)	22.2

Data are *n* or means ± SD.

Table 2—*Selected characteristics of Navajo women with GDM, Shiprock Hospital, 1983–1987, among women tested for NIDDM compared with those lost to follow-up*

Variable	Tested	Not tested	Significance (P)
n	56	23	
Mean BMI (kg/m²)	31.3	29.2	0.16
Mean parity	2.7	2.82	0.82
Mean GTT total (mmol/l)	35.7	35.1	0.4
Mean infant weight (g)	3,413	3,689	0.06
Mean age (years)	31.3	29.2	0.24
Percent with fasting blood sugar >5.83 (mmol/l)	7	17	0.22
Percent with GTT total >41.63 (mmol/l)	7	4	0.99
Percent with later GDM	67	40	0.25

information from the delivery log book, prenatal registry, and hospital discharge codes, 180 patients were identified with a diagnosis related to "diabetes in pregnancy."

Their charts were reviewed early in 1994 to determine if each case of "diabetes in pregnancy" met the study criteria. Twenty-seven patients had only one elevated plasma glucose level on a GTT and were excluded. Other reasons for exclusion from follow-up included: non-Navajo lineage ($n = 6$), a diagnosis of NIDDM before the onset of the index pregnancy ($n = 21$), and irretrievable or poorly documented records ($n = 15$).

After exclusions, 111 patients remained. Records were reviewed again to collect pertinent data including later onset of clinical diabetes. Criteria established by the World Health Organization were used (18): symptomatic patients with at least one random blood sugar >11.1 mmol/l and asymptomatic patients with two random blood sugars >11.1 mmol/l. Patients who had not developed NIDDM, as documented in the medical record, were offered GTT testing.

A fasting venous blood sample was drawn, and the patient was given a standard 75-g glucose load. Venous blood was drawn 2 h later. Plasma glucose was measured by the glucose oxidase method using the Beckman Synchron CX5.

Glucose tolerance was classified according to standard criteria of the World Health Organization (18). Diabetes was diagnosed if the fasting venous plasma glucose was ≥7.8 mmol/l or the 2-h postload was ≥11.1 mmol/l. Impaired glucose tolerance (IGT) was diagnosed if the fasting venous plasma glucose was <7.8 mmol/l and the 2-h postprandial value was 7.8 to 11.1 mmol/l. All testing was done between April 1994 and April 1995.

Data were analyzed using Statview. A two-tailed Student *t* test was used to compare means of continuous data, and χ^2 analysis or Fisher's exact test was used for categorical data. *P* values < 0.05 were considered significant, and data are expressed as means ± SD.

To estimate the rate of deterioration of glucose tolerance to NIDDM as a function of time, life-table analyses were done using two sets of assumptions (19). In the first set of assumptions, referred to as the more restrictive method, all women with GDM were included in the analysis. Patients were considered withdrawn if they were lost to follow-up before the beginning of the time interval under consideration or if their follow-up GTT did not diagnose NIDDM. That is, if only 6 years had elapsed since a patient's pregnancy, the patient could not contribute information for any time period greater than 5 years. A further assumption was that withdrawals were uniformly distributed within the interval with respect to time of withdrawal, and the subsequent experience of patients withdrawn (i.e., the rate of deterioration of glucose tolerance) was the same as for patients remaining under observation.

The second life-table analysis included only women whose glucose tolerance status was known. Thus, patients lost to follow-up are not considered. In RESULTS, this analysis is referred to as the less restrictive method.

RESULTS — Table 1 shows selected characteristics of the 111 GDM patients. Of the patients, 65% were classified as obese (BMI >29.0) (20). Of the 79 patients whose NIDDM status was unknown, 71% returned for testing. Table 2 compares the tested ($n = 56$) and untested groups ($n = 23$) with variables that have been associated with the recurrence of GDM or later NIDDM.

Figure 1 summarizes the study design and the results of GTT testing. Of 111 patients at the time of the study review, 32 (29%) had already been diagnosed with NIDDM. The remaining patients were scheduled for GTT testing. Fifty-six (71%) of this group returned; 15 additional patients were diagnosed with NIDDM and 17 with IGT. Combining patients with previously diagnosed NIDDM ($n = 32$) with those with newly diagnosed NIDDM ($n = 15$) yields a total of 42% of the original study group with NIDDM and 58% with NIDDM or IGT.

The above estimates of conversion to NIDDM are based on the assumption that none of the untested group would have later developed NIDDM, which is unlikely to be the case. Assuming that there were no significant differences between the tested and the untested groups and that the proportion of women who developed NIDDM or IGT among those tested was similar to that of those lost to follow-up, the estimated proportion with NIDDM for the entire cohort would be 48% and the estimated rate of abnormal glucose tolerance (NIDDM or IGT) would be 69%.

Table 3 shows potential risk factors for NIDDM at the index pregnancy. GDM patients who later developed NIDDM had greater BMIs, parity, GTT totals, and infant weights. Age was not significant. Also noted are the strong associations between GDM and NIDDM for categorical variables: fasting blood glucose >5.83 mmol/l, GTT total values >41.63 mmol/l, and subsequent GDM. Previous spontaneous abortions and insulin use were not associated with later NIDDM.

Life-table models are presented in Fig. 2. The assumption that withdrawal patients

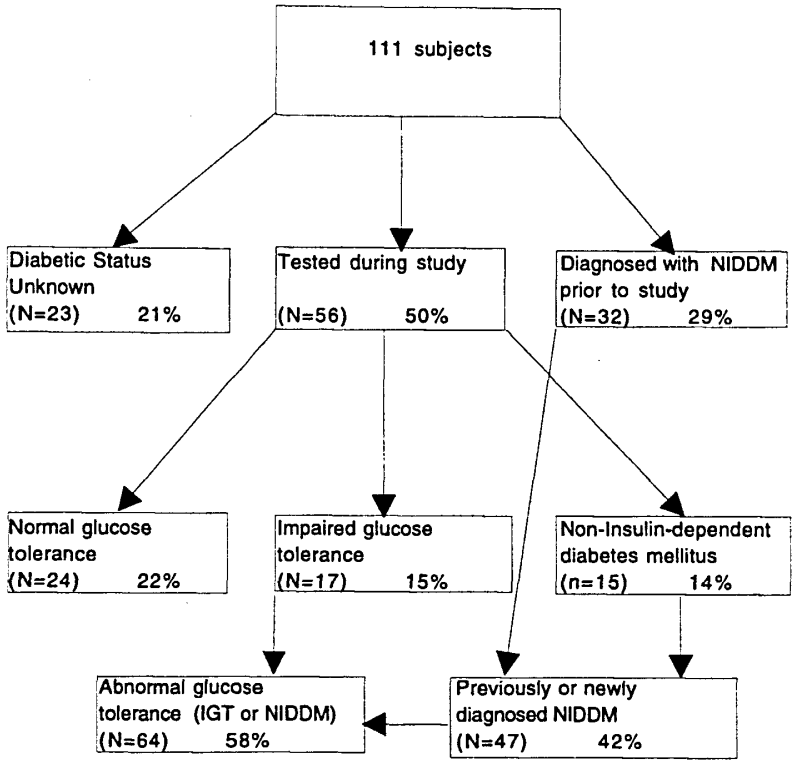

Figure 1—*Glucose tolerance status of eligible Navajo women with GDM, Shiprock Hospital, 1984–1987, as of April 1995.*

are similar to patients who remained in the study is supported by the similarities in key variables above. The more restrictive model, which includes patients lost to follow-up, shows that a patient with a history GDM has a 0.53 probability of developing NIDDM 11 years after her index delivery. The less restrictive model, using only patients whose glucose tolerance status is known, indicates a 0.70 probability of NIDDM after 11 years.

CONCLUSIONS— This study has demonstrated the high prevalence of NIDDM and IGT in Navajo women following a pregnancy with GDM. The diagnosis of IGT has been strongly associated with subsequent progression to NIDDM (61% in Pima Indians after 10 years) (21). While studies vary in methods and populations, the findings of this study are consistent with other results (Table 4).

In 1989, a study from Copenhagen compared 345 GDM patients and control subjects for a mean follow-up time of 5.9 years. Patients with GDM demonstrated a 13% prevalence of NIDDM compared with 0% of control subjects (3). A study in Sweden in 1991 with follow-up time of 3–4 years demonstrated a 3.4% prevalence of NIDDM and 22% of IGT compared with 0% NIDDM and 4% IGT in control subjects (4).

A study from Australia in 1991 compared former GDM patients with controls. With a life-table technique extending to 17 years that made allowances for patients lost to follow-up, GDM patients had a conversion rate to NIDDM of 40% compared with 10% for control subjects (5). A study of Latino women in Los Angeles in 1995 revealed a 55% cumulative incidence rate of NIDDM after 6 years (7).

The highest rate of conversion to NIDDM was noted in Trinidad with a mixed racial population of 157 blacks and East Indians (6). Study patients and those lost to follow-up were similar in ethnic composition and mean age. Follow-up time was 3.5 to 6.5 years. Patient interviews, records, and follow-up GTTs indicated a 62% prevalence of NIDDM and an additional 17% of IGT over the 3.5- to 6.5-year follow-up. However, the study followed only 38% of the original cohort; in the present study, glucose tolerance status was determined for 79% of the study population.

Only two studies have explored the relationship of GDM to NIDDM in Native American women, the first in 1980 in the Pima tribe. The Pima Indians have the highest prevalence of NIDDM in the world (50% in adults over the age of 40). The Pima study was conducted before the initiation of universal GDM screening in the tribe and measured the response in pregnant women without known diabetes to a third-trimester 75-g 2-h GTT as a predictor of subsequent NIDDM. Over the 4- to 8-year follow-up, women whose postprandial glucose was <5.6 mmol/l had a conversion to NIDDM of only 4.5% compared to a 46% conversion rate for women whose postprandial glucose was between 8.9 and 9.4 mmol/l (22).

The other study was conducted among the Zuni. Forty-seven women with a his-

Table 3—*Selected risk factors for later development of NIDDM in Navajo women with a history of GDM, Shiprock Hospital, 1983–1987*

Variable	NIDDM	No NIDDM	Significance (P)	Odds ratio (CI)
n	47	41		
Mean BMI (kg/m^2)	33.49	30.63	0.027	
Mean parity	3.43	2.45	0.023	
Mean infant weight (g)	3701	3353	0.015	
Mean GTT total (mmol/l)	38.3	35.31	0.023	
Mean age (years)	32.7	31	0.143	
Percent with fasting blood sugar >5.83 (mmol/l)	89	43		11.05 (103.4–2.3)
Percent with spontaneous abortions	32	28		1.36 (3.5–0.5)
Percent with GTT total >41.63 (mmol/l)	28	2		15.5 (678.0–2.0)
Percent with recurrent GDM	96	47		24.8 (1,132.2–3.0)
Percent with insulin use	28	12		2.830 (11.2–0.8)

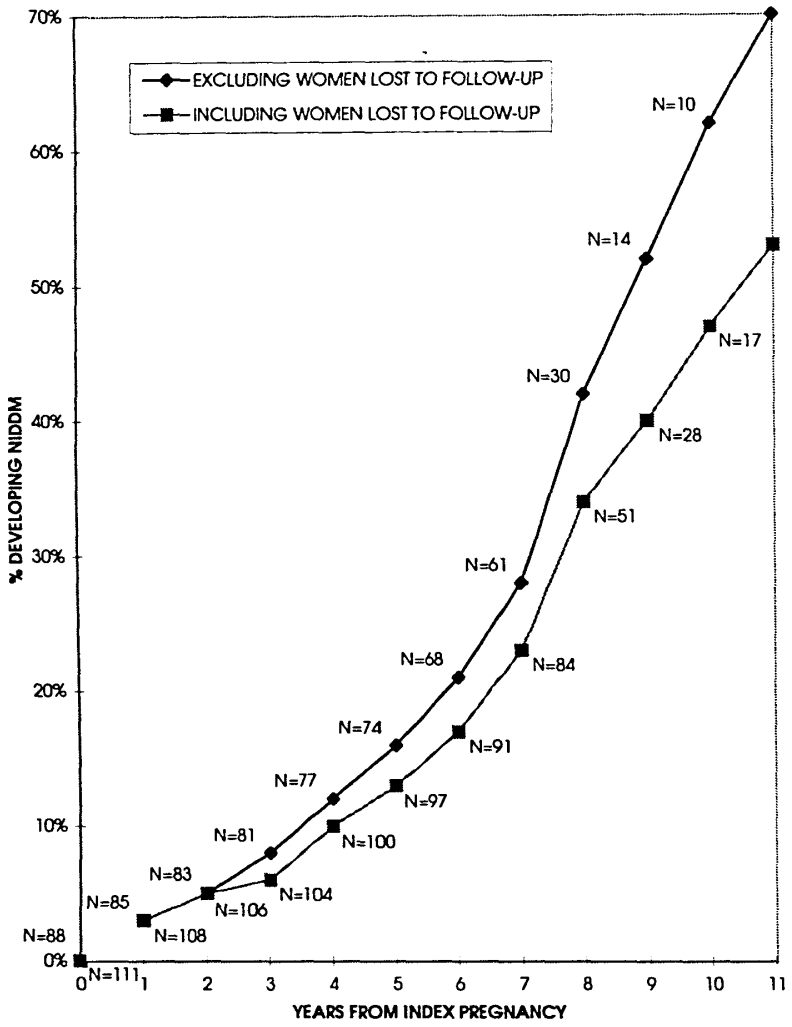

Figure 2—*Life-table for tested patients. Development of NIDDM in Navajo women with a history of GDM.*

tory of GDM were matched to control subjects. Either an elevated random glucose (>11.1 mmol/l) or a formal 75-g GTT was used to diagnose NIDDM after pregnancy. Analysis of data using the Kaplan-Meier survival analysis indicated a 36% conversion to NIDDM in women with a history of GDM compared with 10% in controls at 6 years of follow-up (23).

The prevalence of NIDDM in former GDM patients has not been studied in the Navajo population, although its prevalence in the adult population has. A study done in 1990, screening a small Navajo community, indicated a rising prevalence by age: 5.5%, 26.7%, and 45.7% for women ages 20–44, 45–54, and 55–64, respectively (24). Since the Navajo Nation has a large population, >200,000, more of its members suffer from NIDDM than in smaller tribes with higher prevalence. The incidence of GDM is also high among Navajos: 4.6% (16), compared with 1–3% in the U.S. overall (25).

This is the first study in the Navajo population to examine the prevalence of NIDDM in patients with a history of GDM, and it demonstrates the high risk of subsequent NIDDM in women with a history of GDM. The mean age at diagnosis of NIDDM in former GDM patients was 39.3 years. In the less restrictive life table, by 7 years after delivery, we estimate that 27.7% of this cohort would have developed NIDDM. The life-table curves demonstrate rapidly rising slopes at the 6- to 7-year mark, and it is likely that the rate of NIDDM among women with previous GDM exceeds the rate for the Navajo population of women without a history of GDM.

The study confirms some risk factors for NIDDM. Obesity, recurrence of GDM, severity of GDM (fasting blood glucose >5.83 mmol/l and GTT total >41.63 mmol/l), and higher parity were found to be risk factors. Women who developed NIDDM were older and delivered larger babies. Insulin use and history of spontaneous abortions were not significant.

There are several limitations in the study. The first is the unavailability of a portion of the cohort (21%) for follow-up studies. An attempt is made to address the first limitation and estimate glucose tolerance status for this unknown group. While it seems reasonable to consider both groups, tested and untested, as similar, there may be

Table 4—*Subsequent development of NIDDM and IGT among women with GDM: results from selected studies*

	Follow-up (years)	Conversion to NIDDM (%)	Conversion to IGT (%)	Reference no.	Conversion to NIDDM from life tables	
					6 years (%)	11 years (%)
Pima 1980	4–8	45.5	—	18	—	—
Copenhagen 1989	2–10	13	16	3	—	—
Trinidad 1990	3.5–6.5	62	17	6	—	—
Stockholm 1991	3–4	3.4	22	4	—	—
Melbourne 1991	17	40	—	5	9	18
Zuni 1993	0.5–8	30	—	19	36	—
Los Angeles 1995	6	55	—	7	55	—
Present study 1996	6–11	42	16	—	21	70

factors other than reported variables (BMI, parity, etc.) which could lead to a difference in later NIDDM status, and the limited sample size may have had insufficient power to detect differences in the variables examined in Table 2. The development of the two life tables, more and less restrictive, also addresses this limitation: one table was developed including patients lost to follow-up, and the other included only patients with known glucose tolerance status.

Another limitation is that some patients may have had NIDDM prior to their index pregnancy. Since it was not standard of practice at the time, none of these patients underwent a 75-g 2-h GTT at their 6-week postpartum visit to confirm return to normal glucose tolerance status.

Also, it is important to note that prior to the onset of this research project there was not a regular, annual, recall of former GDM patients for GTT testing. On chart review, it was noted that some of the patients diagnosed with NIDDM prior to the onset of GTT testing often presented with a clinical manifestation of NIDDM at the time of their diagnosis of GDM. It is highly likely that the onset of their NIDDM occurred at an earlier date. Therefore the life-table curves presented in Fig. 2 are an approximation, and in all likelihood they should probably be shifted to the left.

Finally, another limitation may be the changes, noted earlier, concerning screening procedures during the study period, reflecting changing recommendations in the literature. During most of the study period, only high-risk patients were screened at 28 weeks; later all patients were screened. This may have predisposed patient selection toward more severe forms of carbohydrate intolerance. On the other hand, during the early and longer part of the study period, the threshold for an abnormal 1-h screen was 7.2 mmol/l, which was later changed to 7.8 mmol/l, the current standard. The lower threshold may have included patients with milder forms of carbohydrate intolerance. The effect of these changes on study outcome are difficult to quantify, but it is important to note them.

The follow-up of patients with a history of GDM has important health service implications. The potential economic burden of NIDDM for the health care system, much less any one cultural group such as the Navajos, is staggering. The average medical costs per year in 1990 dollars for a woman with NIDDM is $2,834. At the national level, a proposed plan of primary prevention targeted at reducing the conversion to NIDDM by 5% annually would save $179 million over a 10-year period (26).

Women with a history of GDM are excellent candidates for preventive measures. They have been instructed in good nutrition and are practiced in maintaining normal glucose levels. At the postpartum visit, all patients with GDM should receive a 75-g 2-h GTT, and the importance of proper diet and exercise in maintaining ideal body weight, the keystone of preventing NIDDM (27), should be reinforced. Patients with additional risk factors should be followed closely, and it is recommended that all patients with a history of GDM undergo an annual GTT (28).

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