Reproductive History, Glucose Tolerance, and NIDDM in Hispanic and Non-Hispanic White Women

The San Luis Valley Diabetes Study

BETH W. ALDERMAN, MD, MPH
JULIE A. MARSHALL, PHD
EDWARD J. BOYKO, MD, MPH
KATHLEEN A. MARKHAM, MSPH
JUDITH BAXTER, MA
RICHARD F. HAMMAN, MD, PHD

OBJECTIVE— To ascertain whether childbearing would decrease oral glucose-stimulated insulin and C-peptide levels and increase the risk of NIDDM and impaired glucose tolerance in a population of Hispanic and non-Hispanic white women residing in the San Luis Valley of Colorado. Several investigators have related childbearing to subsequent abnormal glucose tolerance.

RESEARCH DESIGN AND METHODS— In a population-based case-control epidemiological study, diabetic patients 20–74 yr of age (n = 196) and randomly sampled control women subjects (n = 735) underwent a glucose tolerance test, a physical examination, and an in-person standardized interview. The relations between the live-birth number and fasting and oral glucose stimulated glucose, insulin and C-peptide concentrations, and NIDDM and impaired glucose tolerance were estimated using linear or logistic regression to adjust for extraneous variables.

RESULTS— In women selected as control subjects, the live-birth number was related to a significant decrease in the sum of 1- and 2-h C-peptide concentrations (coefficient = −0.077, $P < 0.001$) and the logarithm of the sum of 1- and 2-h insulin concentrations (coefficient = −0.014, $P = 0.02$). After adjustment for subscapular skin-fold thickness, the relative odds of NIDDM for the live-birth number, which was small and of borderline significance, diminished (odds ratio = 1.04 for one birth, $P = 0.18$). Findings were similar for impaired glucose tolerance.

CONCLUSIONS— Childbearing was related to lower C-peptide and insulin levels in Hispanic and non-Hispanic women of the San Luis Valley. It had little apparent effect on later risk of NIDDM or impaired glucose tolerance.

From the Department of Epidemiology, University of Washington School of Public Health, Seattle; the Department of Medicine, University of Washington School of Medicine and Medical Service, Veterans Affairs Hospital Medical Center, Seattle, Washington; and the Department of Preventive Medicine and Biometrics, University of Colorado School of Medicine, Denver, Colorado.

Address correspondence and reprint requests to Beth W. Alderman, MD, MPH, Department of Epidemiology, SC-36, University of Washington School of Public Health, Seattle, WA 98195.

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NIDDM, non-insulin-dependent diabetes mellitus; IDDM, insulin-dependent diabetes mellitus; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; RIA, radioimmunoassay; CV, coefficient of variation; BMI, body mass index; WHO, World Health Organization; ANCOVA, analysis of covariance; CI, confidence interval; OR, odds ratio.

During recent years it has become clear that childbearing exerts important and lasting effects on women's health. Reproductive events have been shown to affect later hormone secretion (1) and influence the occurrence of reproductive cancers (2) and other chronic diseases (3,4). Much research has been performed on whether childbearing increases the subsequent risk of developing NIDDM. Interest in this association may stem from two observations: a higher NIDDM prevalence among parous women in a clinical series (5) and a pregnancy-induced insulin-resistant state that frequently results in the appearance of gestational diabetes (6). Pregnancy may also lead to a long-term increase in body weight (7), thereby indirectly increasing the risk of NIDDM.

A recent publication described 25 studies that directly examined the long-term effects of childbearing on glucose tolerance and the occurrence of NIDDM (8). Of these studies, 13 found no association, whereas the remainder found adverse effects of childbearing on glucose tolerance. Only three of these studies simultaneously considered the confounding effects of age and adiposity (9–11), which are known risk factors for the most common type of diabetes—NIDDM (12). Of these, two found a higher prevalence of NIDDM in relation to childbearing, whereas one did not.

Given the inconclusive nature of the data on childbearing and later glucose tolerance, we examined the potential association between childbearing and glucose tolerance in Hispanic and non-Hispanic white women who participated in a population-based epidemiological study of NIDDM in Colorado's San Luis Valley. Because women in this population bear many children and have a high frequency of abnormal glucose tolerance, we hypothesized that childbearing would be related to IGT and NIDDM. We further hypothesized that because fasting and glucose-stimulated insulin

concentrations are elevated in insulin-resistant subjects (13–15) and high-risk ethnic groups (16–18), childbearing would, in this population, be positively related to fasting and glucose stimulated insulin and C-peptide concentrations.

RESEARCH DESIGN AND METHODS — Patients diagnosed with diabetes were identified between 1984 and 1988 by a periodic review of transaction and discharge summaries for all practices and health-care facilities in the study area, ongoing physician referral, ongoing self-referral, and local public advertisements and presentations. Diagnoses were verified by medical record review. Cases were excluded if they were <20 or >74 yr of age, resided outside Alamosa or Conejos Counties, were mentally incompetent, or did not speak English or Spanish. Of the 293 eligible case women identified, 240 (81.9%) participated.

Control women were randomly sampled by a geographically based multistage process. In 1983 and again in 1986, Alamosa and Conejos Counties in southern Colorado were surveyed thoroughly by study staff to identify all occupied structures. A random sample of 3582 houses (57.1% of the occupied structures) was selected to be surveyed for the age, sex, ethnicity, and diabetes history of each occupant. Study staff successfully enumerated the occupants of 3432 houses (95.8%). Occupants were ineligible if they were <20 or >74 yr of age, were living in an institution (school, nursing home, prison), were judged mentally incompetent by study staff, spoke neither English or Spanish, had been told by a physician that they had diabetes, or moved out of the study area before attending the clinic. Occupants were classified as Hispanic if the respondent answered yes to the 1980 census question "Are you (is he/she) of Spanish/Hispanic origin or descent?" A stratified random sample of eligible control women was selected to approximate the distribution of prevalent cases of diabetes with regard to age (10-yr age group), ethnicity (Hispanic or non-Hispanic white), and county of residence (Alamosa or Conejos). Of the 1032 eligible women invited to participate, 735 (71.2%) attended the clinic. Enumeration, characteristics of nonparticipants, and diabetes prevalence for 1984 to 1986 are described in detail elsewhere (19).

Data collection

After informed consent had been obtained, participants attended a study clinic for an OGTT, interview, and physical examination. Participants who reported at least an 8-h fast gave a fasting blood sample; drank a flavored, carbonated, noncaffeinated drink containing 75 g of glucose (Koladex, Orangedex; Custom Laboratories, Baltimore, MD); and then gave blood samples 1 and 2 h later. Before the OGTT, 98% of subjects had fasted ≥10 h, 83% had fasted ≥12 h, and 1.6% had fasted ≥16 h. Subjects with a fasting glucose >14.0 mM did not receive oral glucose or later blood samples unless requested by their physician.

The samples were analyzed for glucose, insulin, and C-peptide concentrations. Plasma glucose was measured by the glucose oxidase method (20), serum insulin by double antibody RIA (21), and plasma C-peptide in the laboratory of Dr. Arthur Rubenstein (22). The serum insulin CVs were 5% within assay and 12% between assay with a minimum concentration of detection <14 pM. The C-peptide CVs were 8% within assay and 12% between assay with a minimum concentration of detection of 0.01 nM.

Trained interviewers administered a standard interview that included questions on potential determinants of glucose, insulin, and C-peptide concentrations such as demographic characteristics, family history of diabetes, body weight at age 20, maximum weight, and numbers of live and nonlive births including abortions, miscarriages, and stillbirths. Two trained observers collected information on height; body weight; arm, waist, iliac, and thigh circumferences; and triceps, subscapular, suprailiac, and lateral calf skin-fold thicknesses. The waist circumference was measured at the tenth rib anteriorly, and the hip circumference was measured at the most lateral aspect of the iliac crest. Skin-fold thicknesses were taken to the nearest 0.1 mm on the participant's right side while she was standing.

Criteria for NIDDM and IGT

Results of the OGTT were used to classify participants into those with NIDDM, IGT, and NGT based on WHO criteria (23). Subjects were also considered diabetic if they used insulin or oral hypoglycemic medication. Subjects with missing data were excluded unless they met WHO criteria for "diabetes unlikely", namely a fasting or casual level <5.7 mM. In this case, they were classified as having NGT.

Diabetic subjects were classified into those who were insulin-dependent or non-insulin-dependent. Subjects were classified as insulin-dependent if their fasting and 1-h and 2-h postglucose load concentrations of C-peptide were <0.1 nM, if the 1-h and 2-h samples were missing but the fasting value was <0.1 nM, or if they lacked data on C-peptide but were diagnosed before 18 yr of age. Of the diabetic subjects, 12 were classified as having IDDM and were excluded from the study.

Definition of variables

Participants were considered to have a family history of diabetes if they reported diabetes in a parent or any sibling. BMI was calculated as current measured weight in kilograms divided by height in meters squared; BMI at 20 yr of age was calculated as reported weight at age 20 in kilograms divided by current measured height in meters squared. The waist-to-hip ratio was calculated as waist circumference divided by hip circumference. Skin-fold thicknesses were the averages of two measurements. Centrality index was calculated as the average subscapular skin-fold thickness divided by the average triceps skin-fold thickness. Non-

live births included stillbirths, miscarriages, and abortions.

Because insulin concentrations were not normally distributed, the natural logarithms of the insulin concentrations were used for all analyses. The OGTT-stimulated concentration of insulin was represented by the natural logarithm of the sum of the 1-h and 2-h post-oral glucose load concentrations, hereafter referred to as the insulin sum logarithm. The OGTT-stimulated concentrations of glucose and C-peptide were represented in the statistical analyses by the sums of their 1-h and 2-h post-oral glucose load concentrations and are hereafter referred to as the glucose sum and the C-peptide sum.

Statistical analysis

Multiple regression methods were used to examine the effects of the live-birth number on each of 8 outcomes: NIDDM; IGT; fasting glucose, insulin, or C-peptide concentrations; and glucose sum, insulin sum logarithm, or C-peptide sum. For each outcome, a causal-modeling approach was used in which only the variable of interest (live-birth number), sampling variables (age, ethnicity, and county of residence), and any additional confounders or effect modifiers were included as explanatory variables (24). The sampling variables were included in all analyses because failure to adjust for their effects could have biased the results (25). A confounder was defined as a risk factor for abnormal glucose tolerance that changed the coefficient for the live-birth number by ≥10% (26). In the absence of prior hypotheses regarding effect modifiers, an effect modifier was defined as a risk factor for abnormal glucose tolerance for which the interaction term with the live-birth number was significant at the $\alpha = 0.05$ level. Variables considered as potential confounders and as potential effect modifiers for each of the outcomes were: subscapular skinfold thickness, BMI, waist-to-hip ratio, centrality index, highest reported body weight, BMI at 20 yr of age, and family history. Also considered as potential effect modifiers were the sampling variables of age and ethnicity. To test for nonlinearity of the effect of the live-birth number on each outcome, the square or natural logarithm of the live-birth number was included in at least one model. Continuous variables were entered as such except where otherwise indicated.

In all control women, multiple linear regression analysis was used to evaluate the association between the live-birth number and the fasting concentrations and sums of glucose, insulin, and C-peptide. In models of the glucose, insulin, and C-peptide sums, the respective fasting concentrations were included as covariables to adjust for baseline incremental differences. In some models of insulin and C-peptide sums, the glucose sum was also included as a covariable to adjust for any differences in glucose concentration after a 75-g oral glucose load. The least-squares method was used to calculate linear regression parameter estimates (27). The residuals were evaluated to identify heteroscedasticity or nonlinearity. The final model was repeated in two subgroups of women: *1*) those with NGT or IGT but not NIDDM, and 2) those with NGT only.

ANCOVA was used to estimate the adjusted means of glucose, insulin logarithm, and C-peptide concentrations for categories of the live-birth number in control women (27). Those categories were: 0, 1–3, 4–6, 7–9, 10–12, and ≥13. Confounders identified in the causal modeling analyses were included as covariables.

In women with NGT or NIDDM, the relative odds of NIDDM in relation to the live-birth number was estimated using multiple logistic regression to adjust for sampling variables and confounders. For some analyses, the live-birth number was grouped as 0, 1–3, 4–6, 7–9, 10–12, and ≥13. The relation between the live-birth number and IGT was analyzed in an analogous manner. We analyzed women with IGT and NIDDM separately because of our expectation that IGT would be heterogeneous with regard to etiology and could differ from NIDDM with regard to risk factors.

RESULTS — Of the 293 women who were identified as potentially being diabetic through medical records or self-report, 240 (81.9%) participated. Of the 240, 196 (81.7%) were confirmed as having NIDDM. A total of 735 (71.2%) of 1032 women sampled by population survey also attended the clinic during the two phases of the study. Of the 735 who attended the clinic, 48 (6.5%) had undiagnosed NIDDM, 104 (14.1%) had IGT, and 583 (79.3%) had NGT. In this group, older women and Hispanic women had higher glucose and C-peptide sums and greater numbers of live births (Table 1). Hispanics and non-Hispanics reported different characteristics with regard to education (means of 10.8 and 13.2 yr, respectively), subscapular skin-fold thickness (means of 26.6 and 21.7 mm, respectively), annual income <$10,000 (43 and 18%, respectively), and a family history of diabetes (41 and 25%, respectively).

Reproductive history and glucose tolerance

In the control women, univariable linear regression analysis showed small but significantly positive associations between the live-birth number and the logarithm of fasting insulin concentration ($\beta = 0.0316$, $P < 0.001$), fasting C-peptide concentration ($\beta = 0.0134$, $P = 0.013$), and fasting glucose concentration ($\beta = 0.0413$, $P = 0.004$). After adjustment for age, ethnicity, and county of residence, these associations became smaller and nonsignificant ($\beta = 0.0132$, $P = 0.151$; $\beta = 0.0028$, $P = 0.630$; and $\beta = 0.0261$, $P = 0.092$, respectively). The associations were even smaller or negative after adjustment for subscapular skin-fold thickness and, for glucose, highest nonpregnant weight (Table 2). After further adjustment for fasting glucose, coefficients for the logarithm of the fasting insulin and the C-peptide con-

Table 1—*Mean values for selected characteristics of 714 women participants randomly selected as control subjects from a Colorado population in a 1984–1988 epidemiological study of diabetes*

		Number of births			1-h and 2-h OGTT stimulated	
	n	Live	Other†	BMI (kg/m²)*	Glucose (mM)	C-peptide (nM)
Age (yr)						
Hispanic Women						
20–29	11	1.4	0.4	21.3	11.1	4.4
30–39	51	2.8	0.5	25.8	13.2	5.3
40–49	58	4.1	0.5	26.7	14.5	5.1
50–59	89	5.1	0.8	27.2	16.1	5.9
60–69	67	5.2	0.8	27.1	17.3	6.6
70–74	30	5.5	0.7	27.0	18.6	6.8
Total	306	4.5	0.7	26.6	15.7	5.8
Non-Hispanic Women						
20–29	7	1.3	1.0	22.9	10.1	3.7
30–39	57	2.4	0.6	24.6	11.4	4.2
40–49	83	2.8	0.7	24.9	11.7	4.4
50–59	131	4.0	0.6	26.3	14.3	4.9
60–69	97	3.7	0.7	25.6	14.4	5.7
70–74	33	3.2	0.9	27.3	16.2	6.2
Total	408	3.4	0.7	25.6	13.5	5.0

The table excluded 21 women who lacked data on live-birth number (2), 2-h glucose (8), 2-h insulin (3), 2-h C-peptide (2), 1-h glucose (2), 1-h C-peptide (1), and subscapular skin-fold thickness (3).
*Based on measurements taken during the clinic visit.
†Sixty-seven women who lacked data on the number of other births were excluded.

centrations were close to zero ($\beta = -0.0009$, $P = 0.903$ and $\beta = -0.0052$, $P = 0.299$, respectively). Exclusion of subjects with NIDDM or NIDDM and IGT had no substantial effect on the results (data not shown).

Univariable linear regression analysis in control women also showed significantly positive associations between the live-birth number and the insulin sum logarithm ($\beta = 0.0234$, $P = 0.003$) and the glucose sum ($\beta = 0.3712$, $P < 0.001$) and a positive, but nonsignificant, relation to the C-peptide sum ($\beta = 0.0344$, $P = 0.227$). After adjustment for age, ethnicity, and county of residence, however, the live-birth number was significantly and inversely related to the C-peptide sum ($\beta = -0.0602$, $P = 0.035$), inversely but nonsignificantly related to the insulin sum logarithm ($\beta = -0.0038$, $P = 0.638$), and positively but nonsignificantly related to the glucose sum ($\beta = 0.1348$, $P = 0.094$). After adjustment for subscapular skin-fold thickness, the associations were stronger for the insulin sum logarithm and the C-peptide sum ($\beta = -0.0131$, $P = 0.068$, and $\beta = -0.0868$, $P = 0.001$ respectively), but weaker for the glucose sum ($\beta = 0.0693$, $P = 0.367$). The associations indicated little change after further adjustment for the respective fasting values (Table 3). For the insulin sum logarithm and the C-peptide sum, additional adjustment by the glucose sum yielded little additional change ($\beta = -0.0141$, $P = 0.019$ and $\beta = -0.0787$, $P < 0.001$, respectively).

Table 2—*Results of multiple linear regression on total number of live births of fasting serum insulin, plasma C-peptide, or plasma glucose concentrations, in 714 Hispanic and Anglo women residing in the San Luis Valley of Colorado*

	Logarithm of fasting insulin (pM)		Fasting C-peptide (nM)		Fasting glucose (mM)	
Variables in model	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
Live births (*n*)	0.0013 ± 0.0080	0.871	−0.0037 ± 0.0052	0.480	0.0153 ± 0.0150	0.309
Age (yr)	0.0042 ± 0.0017	0.011	0.0055 ± 0.0011	<0.001	0.0124 ± 0.0031	<0.001
Hispanic ethnicity*	0.1494 ± 0.0420	<0.001	0.0271 ± 0.0274	0.323	0.1763 ± 0.0849	0.038
Residence county†	−0.0411 ± 0.0418	0.326	−0.0465 ± 0.0272	0.088	−0.2092 ± 0.0784	0.008
Subscapular skin-fold thickness‡	0.0289 ± 0.002	<0.001	0.0158 ± 0.0012	<0.001	0.0124 ± 0.0047	0.008
Highest nonpregnant weight	Not a confounder	—	Not a confounder	—	0.0053 ± 0.0016	0.001
Constant	3.1595	—	0.0387	—	3.6382	—

Data are means ± SE. This analysis excluded 21 women who lacked data on live-birth number (2), 2-h glucose (8), 2-h insulin (3), 2-h C-peptide (2), 1-h glucose (2), 1-h C-peptide (1), and subscapular skin-fold thickness (3).
*Coded as 1 for Anglo and 2 for Hispanic ethnicity.
†Coded as 1 for Alamosa County and 2 for Conejos County.
‡Average of two measurements taken in clinic, to the nearest 0.1 millimeter, on the participant's right side while she was standing.

Table 3—*Multiple linear regression analysis on total number of live births of the sums of 1-h and 2-h OGTT-stimulated concentrations of serum insulin, plasma C-peptide, and serum glucose, in 714 Anglo and Hispanic women*

	Logarithm 1-h + 2-h insulin (pM)		1-h + 2-h C-peptide (nM)		1-h + 2-h glucose (mM)	
Variables in model	Coefficient	*P* value	Coefficient	*P* value	Coefficient	*P* value
Live birth (*n*)	−0.0137 ± 0.0060	0.023	−0.0772 ± 0.0230	<0.001	0.0048 ± 0.0503	0.924
Age (yr)	0.0094 ± 0.0013	<0.001	0.0418 ± 0.0049	<0.001	0.0773 ± 0.0106	<0.001
Ethnicity*	0.1769 ± 0.0319	<0.001	0.7127 ± 0.1208	<0.001	1.3459 ± 0.2634	<0.001
Residence county†	−0.0551 ± 0.0315	0.081	−0.3822 ± 0.1204	0.002	0.2081 ± 0.2634	0.430
Subscapular skinfold thickness‡	0.0087 ± 0.0017	<0.001	0.0238 ± 0.0061	<0.001	0.0736 ± 0.0123	<0.001
Fasting value§	0.4827 ± 0.0283	<0.001	2.5948 ± 0.1655	<0.001	0.2126 ± 0.0069	<0.001
Constant	3.8218		0.7070		−14.3887	

Data are means ± SE. This analysis excluded 21 women who lacked data on live-birth number (2), 2-h glucose (8), 2-h insulin (3), 2-h C-peptide (2), 1-h glucose (2), 1-h C-peptide (1), and subscapular skin-fold thickness (3).

*Ethnicity coded as 1 for Anglo and 2 for Hispanic ethnicity.

†Residence county coded as 1 for Alamosa County and 2 for Conejos County.

‡Average of two measurements taken in clinic, to the nearest 0.1 millimeter, on the participant's right side while she was standing.

§For the logarithm of the 1-h plus 2-h insulin, the fasting value is insulin logarithm; for the 1-h + 2-h C-peptide, the fasting value is C-peptide; for the 1-h + 2-h gl ucose, the fasting value is glucose.

Results of the ANCOVA (Figs. 1–3) show the decrement in the adjusted mean values of the C-peptide sum with increasing numbers of live births. A smaller decrement is observed for the insulin sum logarithm, whereas no change is observed for fasting values of glucose, insulin, or C-peptide or in the glucose sum.

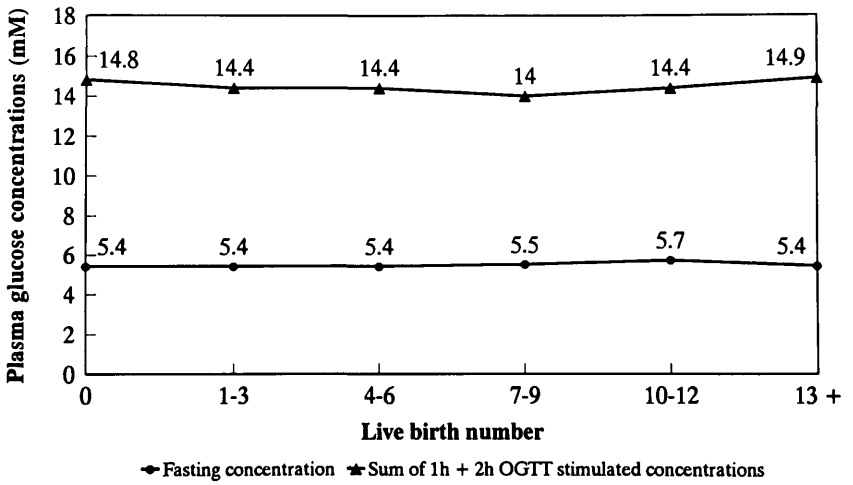

Figure 1—*The mean of the fasting and the sum of the 1-h and 2-h post-oral glucose load serum glucose concentrations (mM) by the live-birth number, adjusted for age, ethnicity, county of residence, and subscapular skin-fold thickness. The fasting level was adjusted for highest reported weight; the sum was also adjusted for the fasting C-peptide concentration.*

Reproductive history, NIDDM, and IGT

Univariable logistic regression analyses showed significant increases in the risk of NIDDM and IGT in relation to the live-birth number (respective odds ratios with 95% CIs were: 1.18, 1.1–1.2; 1.11, 1.03–1.19). After adjustment for confounding by the sampling variables age, ethnicity, and county of residence, however, the risk estimates were lower and of borderline significance for NIDDM only (respective ORs with 95% CIs were: 1.06, 1.00–1.12; 1.03, 0.95–1.12). After further adjustment for BMI or subscapular skin-fold thickness, the risk of NIDDM or IGT associated with an increase in the live-birth number was small and nonsignificant (Table 4). The risk of NIDDM did not increase monotonically across live-birth number categories (as compared with no live births, the ORs with 95% CIs were: 0.58, 0.28–1.23 for 1–3 live births; 0.64, 0.30–1.37 for 4–6 live births; 0.79, 0.34–1.82 for 7–9 live births; 1.58, 0.54–4.61 for 10–12 live births; and 0.95, 0.23–3.83 for ≥13 live births). Results were similar for risk of IGT (data not shown).

CONCLUSIONS— In univariable analyses, the live-birth number was positively related to both fasting and OGTT-stimulated concentrations of glucose, insulin, and C-peptide. However, these relations were mostly accounted for by the older age and Hispanic ethnicity of women with more live births. Unexpectedly, after accounting for the effects of

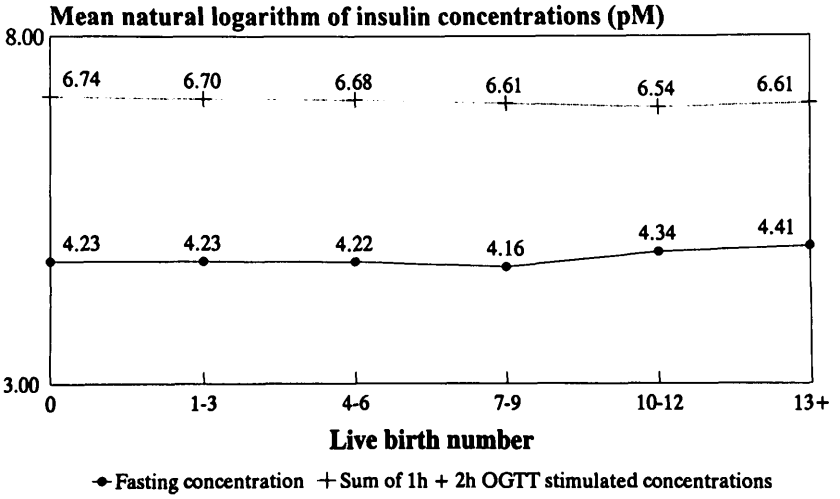

Figure 2—*Mean logarithm of the fasting and the sum of the 1-h and 2-h post-oral glucose load serum insulin concentrations (pM) by the live-birth number, adjusted for age, ethnicity, county of residence, and subscapular skin-fold thickness. The sum was also adjusted for fasting insulin concentration.*

age, ethnicity, and county of residence, childbearing was associated with a significant decrease in the insulin and C-peptide responses to an oral glucose load. Further adjustment for indicators of body fat strengthened these associations.

A similar pattern was observed in analyses of childbearing and the risks of NIDDM and IGT. After accounting for the effects of age, ethnicity, and county of residence, the estimated effects of childbearing were small and of borderline significance for NIDDM only. The latter effect diminished slightly after accounting for the effects of body fat. Because future risk of NIDDM correlates positively with 2-h OGTT-stimulated plasma insulin concentration (28), the observed lack of effect of the live-birth number on NIDDM is consistent with the association between childbearing and lowered insulin and C-peptide responses.

Despite the absence of a significantly positive association, we cannot rule out the existence of a small effect that could be substantial in women with many children and also large enough to be of public health significance in women of the San Luis Valley. Although the relative odds of NIDDM, 1.04 per live birth, is lower than the 1.16 observed in a previous study (9), the CI indicated that the effect of a single live birth was unlikely to be <0.98 and could be as high as 1.11. The estimates for IGT were similar. Perhaps, in this population, where Hispanic men and women are at high risk of NIDDM for other reasons, the relative effect of childbearing is smaller than in other populations and therefore more difficult to detect.

The effect of childbearing on C-peptide and insulin responses could be mediated through a variety of mechanisms. One such mechanism could be a decrease in the resistance to insulin action (14). Because pregnancy results in a long-term decline in serum prolactin concentration (1), and because hyperprolactinemia is associated with abnormally high stimulated glucose and insulin concentrations (29,30) with decreased insulin binding to adipocytes from pregnant women (31), childbearing could conceivably lead to prolactin-related insulin sensitivity. Our observation that C-peptide and insulin responses decreased with live-birth number, even at the same level of glucose, is consistent with this hypothesis. On the other hand, we know of no reports that the risk of NIDDM or IGT decreases with childbearing, nor any evidence that insulin sensitivity increases in response to the long-term reduction in serum prolactin which follows pregnancy.

Childbearing might also affect glucose tolerance through pancreatic exhaustion. The insulin resistance induced by pregnancy (6,32) could contribute to the demands on the pancreas that, according to current theories, lead to pancreatic β-cell insufficiency and NIDDM (33). The observed decrease in insulin

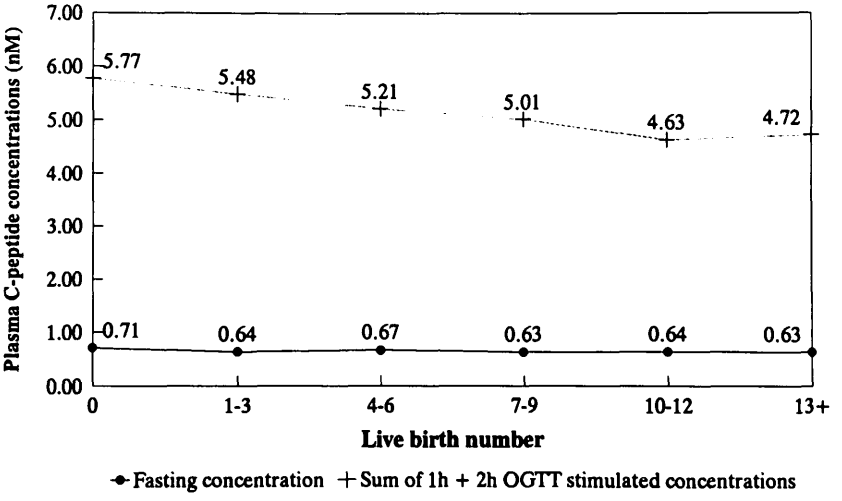

Figure 3—*Mean of the fasting and the sum of the 1-h and 2-h plasma C-peptide concentrations (nM) by the live-birth number, adjusted for age, ethnicity, county of residence, and subscapular skin-fold thickness. The sum was also adjusted for fasting C-peptide concentration.*

Table 4—*Results of multiple logistic regression of NIDDM or IGT on live-birth number, adjusted for sampling strata (age; ethnicity; county of residence) and confounders (subscapular skin-fold thickness; BMI), in women with NIDDM, IGT, and NGT*

Variable	NIDDM OR (95% CI)	IGT OR (95% CI)
Live-birth number	1.04 (0.98, 1.11)	1.01 (0.93, 1.10)
Age at clinic visit (yr)	1.07 (1.06, 1.09)	1.04 (1.02, 1.06)
Hispanic ethnicity*	3.41 (2.31, 5.05)	1.78 (1.12, 2.83)
County of residence†	0.61 (0.42, 0.90)	0.95 (0.59, 1.51)
BMI (kg/m^2)‡	Not a confounder	1.14 (1.10, 1.19)
Subscapular skin-fold thickness§	1.09 (1.07, 1.11)	Not a confounder

Subjects were excluded if they lacked data on live-birth number (2) or average subscapular skin-fold thickness (3); for women with NIDDM $n = 243$; for women with IGT $n = 104$; and for women with NGT $n = 579$.

*Coded as 1 for Anglo and 2 for Hispanic ethnicity.

†Coded as 1 for Alamosa County and 2 for Conejos County.

‡Based on measurements taken during the clinic visit.

§Average of two measurements taken in clinic, to the nearest 0.1 millimeter, on the participant's right side while she was standing.

and C-peptide responses with increasing numbers of pregnancies is consistent with this hypothesis: If increased pancreatic demand leads to β-cell insufficiency, the more frequent the periods of increased demand, the greater should be the insufficiency. The small, though nonsignificant, increase in OGTT-stimulated glucose concentrations observed here is also consistent with this possibility, as is the above-noted increase in risk of NIDDM, which, though small and nonsignificant in this study, has been observed previously (9).

Other potential explanations for a decrease in the insulin and C-peptide response after childbearing include changes in the kinetics of C-peptide distribution or its clearance rate, alteration in gut glucose absorption, and release of gastrointestinal hormones that inhibit or promote insulin secretion (34,35). To our knowledge, these phenomena have not been studied in relation to childbearing. The possible long-term effects of lactation on insulin resistance and secretion are also unknown.

The small effect of childbearing on NIDDM risk observed in these data would be statistically significant only in an impractically large study. Our study may, however, have underestimated the effect of childbearing on NIDDM. For example, if only a subgroup of women were affected by childbearing, then the results of this and previous studies may have yielded falsely low estimates. Our findings suggest that women who are heavier in the early childbearing years may be the ones who are at risk of NIDDM caused by childbearing (data not shown). This finding is believable in the context of the pancreatic exhaustion hypothesis in that pregnancy could conceivably cause more damage to the pancreas in obese women than in lean women. Such findings are difficult to evaluate statistically because, in the analysis of multiple subgroups, the sample sizes are small and the number of subgroups high. In addition, in the predominantly Catholic and Mormon population of the San Luis Valley, older women who had very few (or very many) children may be biologically different and may show a different risk of NIDDM in relation to childbearing. In our data, after adjustment for body weight, we observed an increase in the risk of NIDDM with childbearing except in the lowest and highest live-birth number categories.

The associations observed in previous studies may, on the other hand, be spurious. We found that several risk factors for NIDDM, such as age, ethnicity, and body weight, were strongly related to childbearing. In other populations, childbearing has possibly been related to NIDDM because both are influenced by body weight. In such instances, an observed relation between childbearing and NIDDM would not be directly causal.

The relations between childbearing, glucose tolerance, and NIDDM could be further clarified in a study that includes data on lifetime changes in body weight, body weight distribution, and a more complete history of the determinants and sequellae of childbearing and lactation. Further investigation of the long-term hormonal effects of childbearing may also be enlightening.

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