

Association of Parity With Risk of Type 2 Diabetes and Related Metabolic Disorders

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OBJECTIVE — The relationship between parity and risk of diabetes is controversial, and little information is available regarding associations between parity and measures of insulin resistance and β -cell function. The objective of this study was to investigate the association between parity and risk of glucose intolerance and related metabolic disorders using data from a population-based study in a Native Canadian community.

RESEARCH DESIGN AND METHODS — Female participants ($n = 383$, aged 12–79 years) provided fasting blood samples for the determination of glucose, insulin, C-peptide, and proinsulin concentrations. A 75-g oral glucose tolerance test was administered, and diabetes and impaired glucose tolerance were diagnosed according to World Health Organization criteria. Waist circumference and percent body fat were determined. Information regarding occurrence of live births and previously diagnosed diabetes was obtained from interviewer-administered questionnaires.

RESULTS — Parity was associated with a significantly reduced risk of diabetes (nulliparous vs. ≥ 1 birth, odds ratio 0.43, 95% CI 0.19–0.94, $P < 0.05$) after adjustment for age and waist circumference. In addition, nondiabetic nulliparous women had significantly elevated concentrations of fasting insulin and proinsulin relative to nondiabetic parous women (all $P < 0.05$) in analyses adjusted for age and waist circumference.

CONCLUSIONS — Our results are consistent with those from other populations experiencing high rates of diabetes and suggest the presence of a diabetes-prone phenotype within the nulliparous subcohort of this population, which may contribute to infertility.

Diabetes Care 25:690–695, 2002

The relationship between parity and risk of type 2 diabetes has been examined in a large number of published studies (1). As pointed out by others (1,2), most reported associations

between parity and diabetes have not been adjusted for age or body adiposity, both of which are likely to be important confounding factors. In the nine studies that have presented results adjusted for

age and adiposity (1–9), the findings have been highly inconsistent: three reported a positive relationship between parity and diabetes risk (3–5), five found no effect (1,2,6,7,9), and one demonstrated a protective association with parity (8). Discordant results have also been reported regarding the effect of parity on measures of insulin sensitivity. Kritiz-Silverstein et al. (10) found that the number of pregnancies had a significant positive association with fasting insulin concentrations as well as an inverse association with an index of insulin sensitivity, after adjustment for waist-to-hip ratio and other covariates. Reports from the Pima and San Luis Valley Diabetes studies, however, documented inverse associations between parity and insulin concentrations (7,8). Recently, Cowan et al. (9) found that parity displayed a quadratic association with fasting insulin concentrations among American Indian women participating in the Strong Heart Study. In addition, the association of parity with measures of β -cell dysfunction, another major disorder in the etiology of type 2 diabetes, has not been investigated. The role of child-bearing in the pathogenesis of diabetes and related metabolic disorders thus remains controversial.

The objective of the present study was to investigate the association of parity with risk of type 2 diabetes and related metabolic disorders, including elevated insulin and proinsulin concentrations, using data from the Sandy Lake Health and Diabetes Project (SLHDP). Insulin and proinsulin have been shown to be valid surrogate indexes of insulin resistance and β -cell dysfunction, respectively (11,12). The SLHDP is an ongoing population-based epidemiological study of diabetes and associated risk factors that was conducted in partnership with Sandy Lake First Nation, an isolated Native Canadian community in northern Ontario (13,14). Rates of type 2 diabetes and impaired glucose tolerance (IGT) among women in this community are very high (age-adjusted prevalence rates, age 10–79 years: IGT 19.8%, type 2 diabetes

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Received for publication 31 October 2001 and accepted in revised form 20 December 2001.

Abbreviations: CV, coefficient of variation; GDM, gestational diabetes mellitus; HOMA_{IR}, homeostasis model assessment index of insulin resistance; IGT, impaired glucose tolerance; OC, oral contraceptive; OGTT, oral glucose tolerance test; OR, odds ratio; PCOS, polycystic ovary syndrome; SLHDP, Sandy Lake Health and Diabetes Project.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

28.0%), and the age of onset of glucose intolerance is relatively young (14). Furthermore, families in Sandy Lake are large, and women tend to initiate childbearing at an early age. The elucidation of a diabetogenic role for either parity or nulliparity would thus be of substantial public health importance for this community. The following specific research questions were posed: 1) Is parity associated with risk of type 2 diabetes? and 2) Is parity associated with variation in concentrations of insulin and proinsulin among nondiabetic women?

RESEARCH DESIGN AND METHODS

The methodology of the SLHDP prevalence study has been presented in detail previously (13,14). Briefly, between July 1993 and December 1995, 728 of 1,018 (72%) eligible residents of Sandy Lake aged 10–79 years participated in a population-based cross-sectional survey to determine the prevalence of type 2 diabetes and its associated risk factors. Signed informed consent was obtained from all participants, and the study was approved by the Sandy Lake First Nation Band Council and the University of Toronto Ethics Review Committee. The analyses in this study were based on data from 383 Sandy Lake female subjects, aged 12–79 years, for whom information was available on glucose tolerance status and for whom serum specimens were available for determination of insulin and proinsulin.

Participants provided fasting blood samples for glucose, insulin, C-peptide, and proinsulin after an 8- to 12-h overnight fast. A 75-g oral glucose tolerance test (OGTT) was administered, and a second sample for glucose was drawn after 120 min. Individuals were excluded from the OGTT if they had physician-diagnosed diabetes and were 1) currently receiving treatment with insulin or oral hypoglycemic agents or 2) if they had a fasting blood glucose concentration exceeding 11.1 mmol/L. Women who were pregnant at the time of initial contact received their OGTT at least 3 months postpartum. Diabetes and IGT were diagnosed according to World Health Organization criteria (15).

Insulin was measured using a radioimmunoassay technique (Pharmacia), which has a lower detection limit of 22 pmol/L and an interassay coefficient of variation (CV) of 7.2–8.8%. This assay displays a very high degree of cross-

reactivity with proinsulin (100%), and thus the reported values refer to concentrations of total immunoreactive insulin (16). Glucose concentration was measured using the glucose oxidase method (13). C-peptide level was measured using a radioimmunoassay (Diagnostic Products, Los Angeles, CA) with a minimal detection limit of 43 pmol/L and cross-reactivities of 0% with insulin and <13% with proinsulin. Proinsulin was determined using a human proinsulin radioimmunoassay, which has a laboratory sensitivity of 3.5 pmol/L and a CV of 6.2–21.0% (Linco Research, St. Louis, MO). This assay displays 46% cross-reactivity with des 31,32 proinsulin, the major form of circulating split proinsulin, and thus reported values refer to total proinsulin-like materials (17). Cross-reactivity of this assay with des 64,65 proinsulin, insulin, and C-peptide is very low (<0.1%). Proinsulin was measured in serum specimens that had been stored at -70°C for 3–5 years at the Core Lab of the Banting and Best Diabetes Center, University of Toronto. Insulin resistance was estimated from fasting glucose and insulin concentrations using the homeostasis model assessment index (HOMA_{IR}) of Matthews et al. (18). This index has been validated against gold standard measures of insulin resistance (18).

Anthropometric measurements were performed as described previously (13–14). Information on the number of live births and current age of each child was obtained using standardized questionnaires administered by trained interviewers (13). Information regarding abortions, miscarriages, and still births was not collected, and thus “parity” in the present study refers to live full-term births of one or more infant(s). Women with diabetes were also asked about the duration of their diabetes and the current method of treatment (diet, oral hypoglycemic agents, or insulin). Information regarding current use of oral contraceptives (OCs) was obtained, with consent, from medical records maintained at the community clinic.

Statistical analyses

All analyses were carried out using SAS version 6.12 (19). For women with previously diagnosed diabetes, live births that occurred after the onset of the disease were excluded from the calculation of the number of live births to ensure that risk

estimates related to exposures that occurred before the onset of diabetes. The distributions of continuous variables were assessed for normality, and the natural log transformation of skewed variables was used in subsequent multivariate analyses.

The association between parity and risk of diabetes was assessed using multiple logistic regression. We evaluated the risk associated with parity using two different approaches: parity modeled 1) as a continuous variable (risk per one additional live birth) and 2) as a dichotomous variable (nulliparous versus parous). Age-adjusted odds ratios (ORs) were examined, as well as ORs adjusted for age, waist circumference, and use of OCs. We assessed the possibility of a nonlinear effect for number of births in approach (1) by adding a quadratic term to the model. Among nondiabetic women, ANCOVA was used to calculate adjusted mean levels of metabolic variables (including glucose, insulin, HOMA_{IR} , and proinsulin) for nulliparous and parous subjects. Natural logarithms of the dependent variables were used in these analyses, and the results were back-transformed for presentation in the figures, with 95% CIs. In addition, we used linear regression analysis to examine the association of parity (modeled as a continuous variable) with metabolic variables. Quadratic terms were included in these models to assess the possibility of nonlinear associations (9,20). In linear and logistic regression analyses, we adjusted proinsulin concentration for insulin secretion by including C-peptide as a covariate. The rationale for this approach has been described previously (21). Finally, we tested for age-parity interactions in both our logistic and linear regression models by including age-parity interaction terms and by conducting analyses within age strata.

RESULTS — Anthropometric and metabolic characteristics of participants in the current analysis are presented in Table 1. The average age was ~31 years, and the average parity was 2.6 births. The prevalence of glucose intolerance was high, with 14.2% of women having IGT and 18.1% having newly or previously diagnosed diabetes.

Table 2 presents characteristics of SLHDP participants by parity categorized into four levels. Age, waist circumference, and fasting and 2-h glucose concentra-

Table 1—Anthropometric, metabolic, and reproductive characteristics of female participants in the SLHDP (n = 383)*

Variable	Mean	Range
Age (years)	30.97 ± 15.64	12.00–79.96
Number of live births	2.57 ± 2.79	0–14
Fasting glucose (mmol/l)	6.54 ± 3.32	3.7–25.5
2-h glucose (mmol/l)	7.20 ± 4.12	2.6–32.1
Fasting insulin (pmol/l)	140.39 ± 119.97	25–1592
HOMA _{IR}	6.00 ± 7.49	0.77–104.17
Fasting C-peptide (pmol/l)	721.91 ± 450.76	90–4050
Fasting proinsulin (pmol/l)	15.50 ± 11.17	3–94
Percent body fat	42.72 ± 10.31	8.1–61.2
Waist circumference (cm)	91.90 ± 13.35	61.0–142.5
Diabetes (%)	18.1	
IGT (%)	14.2	
Current use of OCs (%)	2.0	

Data are means ± SD, or means, unless otherwise indicated. *Sample sizes vary slightly for specific variables due to occasional missing values.

tions increased across parity categories. HOMA_{IR} and proinsulin concentration displayed U-shaped patterns, with higher concentrations among both nulliparous women and those with five or more live births. Diabetes prevalence increased steadily across parity categories, ranging from 13.2% among nulliparous women to 38.9% among women reporting five or more births. After adjustment for age, trends in metabolic and anthropometric characteristics across parity categories were less clear. However, nulliparous women were distinctive in that they were more insulin resistant, had higher concentrations of fasting and 2-h glucose and proinsulin, and had higher total and regional adiposity compared with parous women (data not shown).

Results of multiple logistic regression

analyses of parity and risk of diabetes are presented in Table 3. Women who had experienced at least one live birth had a significantly reduced risk of diabetes compared with nulliparous women after adjustment for age, waist circumference, and OC use (OR = 0.43, 95% CI 0.19–0.94, $P < 0.05$). Analyses conducted separately for women <30 vs. ≥30 years of age indicated similar patterns of association in these two age categories (data not shown). When analyzed as a continuous variable, the number of births did not appear to be associated with risk of diabetes, nor was there evidence of a quadratic relationship between number of births and risk of diabetes (Table 3).

Among nondiabetic women, those reporting at least one live birth had significantly lower concentrations of fasting

insulin and proinsulin concentrations after adjustment for age, waist circumference, IGT, and OC use ($P < 0.05$ and $P < 0.0001$, respectively) (Table 4). When analyzed as a continuous variable, the number of births was not significantly associated with variation in metabolic traits after adjustment for age, waist circumference, IGT, and OC use (all $P > 0.30$). However, multiple regression models that included both linear and quadratic terms indicated that there were significant inverse nonlinear associations between the number of births and variation in fasting insulin and proinsulin concentrations (linear and quadratic terms for both models, $P < 0.05$). In other words, adjusted concentrations of insulin and proinsulin were highest among nulliparous women, lowest among those at midlevels of parity, and intermediate among those at the highest levels of parity.

CONCLUSIONS— In this study, we have demonstrated that nulliparity is associated with an increased risk of diabetes among women in a Native Canadian population after adjustment for age, waist circumference, and OC use. In addition, nondiabetic nulliparous women had higher concentrations of fasting insulin and proinsulin than parous women after adjustment for covariates. Taken together, our results suggest that both insulin resistance and β -cell dysfunction are elevated in nulliparous compared with parous women in this population. The intermediate concentrations of insulin and proinsulin among highly parous nondiabetic women in the linear regression analyses (i.e., the quadratic association) may indicate that very high levels of parity are

Table 2—Anthropometric and metabolic characteristics of female participants in the SLHDP, stratified by parity category

Variable*	Nulliparous†	1–2 Births†	3–4 Births†	≥5 Births†
n	129	83	99	72
Age	20.53 ± 11.77	27.19 ± 10.18	33.98 ± 9.49	49.87 ± 15.25
Glucose (mmol/l)	6.13 ± 3.03	6.49 ± 3.60	6.39 ± 2.92	7.54 ± 3.84
2-h glucose (mmol/l)	6.41 ± 4.06	6.81 ± 3.87	7.35 ± 3.33	9.08 ± 5.02
Insulin (pmol/l)	150.30 ± 174.21	142.66 ± 96.79	132.26 ± 70.71	131.41 ± 70.62
HOMA _{IR} (units)	6.07 ± 10.14	6.05 ± 6.01	5.51 ± 5.03	6.50 ± 6.30
Proinsulin (pmol/l)	15.97 ± 12.36	15.82 ± 12.95	13.58 ± 8.32	16.94 ± 9.99
Percent body fat	37.62 ± 11.62	44.66 ± 9.06	45.98 ± 7.71	45.01 ± 9.03
Waist (cm)	84.97 ± 14.24	92.84 ± 12.92	95.33 ± 10.01	98.21 ± 10.98
Diabetes (%)	13.2	15.7	16.2	38.9
IGT (%)	6.2	12.1	24.2	19.4
Current use of OCs (%)	0.0	3.6	3.0	2.8

Data are means ± SD or % crude prevalence. *All values fasting unless otherwise indicated; †sample sizes vary for certain variables due to occasional missing values.

Table 3—Association between parity and risk of diabetes in the SLHDP*

Independent variable	Adjusted for age			Adjusted for age, waist circumference, and OC use		
	OR	95% CI	P	OR	95% CI	P
Nulliparous vs. parous†	0.49	0.23–1.02	0.0562	0.43	0.19–0.94	0.0355
Number of Births‡	0.93	0.83–1.05	0.2303	0.94	0.83–1.06	0.2888

*OR and 95% CI were estimated using logistic regression analysis; †codes: 0 = nulliparous, 1 = parous; ‡continuous variable, OR refers to increase in risk per additional live birth; test of quadratic relationship, $P = 0.30$.

also associated with poorer insulin sensitivity and β -cell function, perhaps through a separate physiological mechanism (5,10).

Our findings are consistent with those from studies in other populations that are known to suffer from high rates of diabetes. Nulliparity was associated with diabetes risk and elevated insulin concentrations among Pima Indian women, a population similar to that of Sandy Lake with respect to both Native North American ethnicity and high diabetes risk (8). In the Strong Heart Study, which includes Native American subjects from a number of regions, diabetes risk and insulin levels displayed quadratic relationships with parity, with the highest levels being among nulliparous and highly parous women (9). Finally, insulin concentrations were inversely associated with parity in the San Luis Valley Diabetes Study cohort, which included a large proportion of Mexican-American subjects (7).

Elevated proinsulin concentration has been proposed as a surrogate indicator of β -cell dysfunction (22). Proinsulin concentrations are elevated among subjects with IGT, type 2 diabetes, and gestational diabetes mellitus (GDM) (23–26), and higher concentrations have been shown to predict the development of diabetes in prospective studies (27–30). Furthermore, previous studies have re-

ported statistically significant correlations between proinsulin concentration and more detailed measures of β -cell function (31–33). In the present study, nondiabetic nulliparous women had proinsulin concentrations that were significantly higher than those among parous women, suggesting that the nulliparity was associated with a relatively higher degree of β -cell dysfunction. To our knowledge, this is the first study to investigate the relationship between parity and proinsulin concentrations in a population-based study, and these findings extend the evidence supporting a connection between nulliparity and insulin resistance, β -cell dysfunction, and diabetes risk.

In interpreting the elevated insulin concentrations and diabetes risk among nulliparous Pima women participating in their study, Charles et al. (8) suggested that hormonal changes associated with insulin resistance could be related to increased risk of conditions causing infertility, including polycystic ovary syndrome (PCOS). This hypothesis is supported by the work of Dunaif et al. (34), who documented lower rates of insulin-mediated glucose disposal in women with PCOS relative to both control subjects and women with type 2 diabetes. In addition, women with PCOS have been shown to be at elevated risk for a number of insulin resistance-related conditions, including

type 2 diabetes, GDM, hypertension, cardiovascular disease, and dyslipidemia (35). Finally, three recent studies have presented evidence of β -cell dysfunction in women with PCOS and related conditions (36–38). Unfortunately, we do not have any information on the underlying determinants of nulliparity in this population, including the prevalence of PCOS or other forms of infertility. Population surveys have indicated, however, that PCOS is highly prevalent among premenopausal women (35) and is associated with obesity and insulin resistance. Our data indicating significantly elevated insulin and proinsulin concentrations in nulliparous women suggests that PCOS or related reproductive disorders might be contributing to nulliparity in this population.

One potential limitation of the present study involves the lack of information on abortions, miscarriages, and stillbirths. However, in a previous study that analyzed risk of diabetes associated with both number of pregnancies and number of live births, the patterns of association were similar between the two exposure measures (5). We also did not have information regarding the presence of a medical history of GDM. In a previous study among the Ojibway and Oji-cree of northwestern Ontario, a previous diagnosis of GDM was associated with a signifi-

Table 4—Mean concentrations of metabolic variables among nondiabetic women in the SLHDP*

Variable	Adjusted for age			Adjusted for age, waist circumference, OC use, and IGT		
	Nulliparous	Parous	P	Nulliparous	Parous	P
Fasting glucose	5.31	5.37	0.49	5.33	5.36	0.75
2-h glucose	5.95	5.65	0.23	5.98	5.58	0.07
Fasting insulin	109.40	108.84	0.95	118.63	103.96	0.048
HOMA _{IR}	3.59	3.61	0.94	3.90	3.44	0.09
Proinsulin†	12.47	10.65	0.006	12.64	10.58	<0.0001

*Adjusted mean concentrations were estimated using ANCOVA; †proinsulin also adjusted for C-peptide (see RESEARCH DESIGN AND METHODS).

cant increased risk of subsequent GDM (39). Thus, it seems highly unlikely that previous GDM explains the decreased diabetes risk among parous women in the present study.

In conclusion, we have demonstrated that nulliparity is associated with an increased risk of type 2 diabetes and that nulliparous women had higher concentrations of insulin and proinsulin than parous women. These results suggest the presence of a prevalent diabetes-prone phenotype within the nulliparous subcohort of this population and indicate that these women should be considered to be at increased risk of developing type 2 diabetes and related metabolic disorders.

Acknowledgments—This work was supported by grants from the National Institutes of Health (91-DK-01 and 1-R21-DK-44597-01) and the Ontario Ministry of Health (04307). Dr. Hanley was supported by Health Canada through a national health research and development program research training award and by the Canadian Institutes of Health Research (postdoctoral fellowship). Dr. Harris is a Career Scientist with the Ontario Ministry of Health. Dr. Hegele is a Career Investigator of the Heart and Stroke Foundation of Ontario (2729).

The authors would like to acknowledge the following groups and individuals, whose cooperation was essential in the design and implementation of this project: the chief and council and community members of Sandy Lake First Nation, the Sandy Lake community surveyors (Louisa Kakegamic, Tina Noon, Madeliene Kakegamic, Elda Anishinabie, Annette Rae, Connie Kakegamic, and Mary Mamakeesic), the Sandy Lake nurses, the staff of the University of Toronto Sioux Lookout Program, the Department of Clinical Epidemiology of the Samuel Lunenfeld Research Institute, Dr. Alexander Logan, and Annette Barnie.

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