The Relationship of Menstrual Irregularity to Type 2 Diabetes in Pima Indian Women

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OBJECTIVE — Menstrual irregularity is associated with hyperinsulinemia and hyperandrogenemia in nondiabetic Pima Indian women of child-bearing age. In this population-based study, we determined the relationship of menstrual irregularity to type 2 diabetes in Pima Indian women.

RESEARCH DESIGN AND METHODS — Participants for this cross-sectional analysis were 695 nonpregnant Pima Indian women, aged 18–44 years, involved in an ongoing epidemiologic study of diabetes among residents of the Gila River Indian Community of Arizona. Clinical data were collected by questionnaire and an examination that included a 75-g oral glucose tolerance test; diabetes was diagnosed by World Health Organization criteria. Menstrual irregularity was defined as an interval of 3 months or more between menses, when not pregnant, since age 18 years.

RESULTS — History of menstrual irregularity was significantly associated with a high prevalence of diabetes (37 vs. 13%; odds ratio = 4.2, 95% CI = 1.6–10.8) in the least obese women (BMI < 30 kg/m^2), adjusted for the effects of age and overall obesity. This association was, in part, because of greater central obesity in women with irregular menses. In more obese women, there was little association with menstrual irregularity, and diabetes was frequent regardless of menstrual history.

CONCLUSIONS — Prevalence of type 2 diabetes is higher among Pima Indian women with a history of menstrual irregularity. The difference is most pronounced among the least obese group of women. This association may be because of insulin resistance and hyperinsulinemia, which predict type 2 diabetes, also causing hyperandrogenism and menstrual irregularity. The findings reinforce the need to evaluate women with menstrual irregularity for hyperglycemia.

Type 2 diabetes in Pima Indians is more prevalent in women of reproductive age who have never been pregnant than in those who have had a pregnancy (1). Infertility is also associated with a risk of diabetes in other studies (2,3).

Obesity, a major risk factor for type 2 diabetes, has long been associated with infertility and menstrual abnormalities (4). Obesity, hyperinsulinemia, hyperandrogenemia, and irregular menstruation are also commonly associated with polycystic ovary syndrome (PCOS), the most common endocrine disorder in women of reproductive age (5). In a Swedish long-term follow-up study, women with PCOS experienced not only oligomenorrhea and infertility, but also an increased incidence of hypertension and diabetes (6).

Pima Indians have the world's highest reported prevalence of type 2 diabetes (7) and also have a high prevalence of obesity (8). Furthermore, menstrual irregularity has been associated with hyperinsulinemia and hyperandrogenemia in nondiabetic Pima women of child-bearing age (9). To determine the importance of this finding from a population perspective, we studied the relationship of menstrual irregularity to type 2 diabetes in Pima Indian women.

RESEARCH DESIGN AND METHODS

Women in this study were participants in a longitudinal epidemiologic study of type 2 diabetes and its complications conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) among residents of the Gila River Indian Community of Central Arizona. Since 1965, all residents of the study area at least 5 years old have been invited to participate in research examinations every 2 years, regardless of health status. These biennial examinations include a medical history, physical examination, and an oral glucose tolerance test (10).

Study participants and study design

The cross-sectional analysis included 695 nonpregnant women at their last examination between April 1992 and January 1995 who were 18–44 years old and whose heritage was at least one-half Pima, Tohono O'odham, or a mixture of these two closely related Native American tribes. Examination included measurements of height and weight. Blood pressure was measured once in the supine position with a mercury sphygmomanometer; systolic blood pressure (sBP) and diastolic blood pressure (dBP) were measured to the nearest 2 mmHg at Korotkoff sounds I and IV, respectively. Mean blood pressure (MBP) was defined as two-thirds of the dBP plus one-third of the sBP. Plasma glucose concentration was measured at fasting and 2 h after the 75-g glucose load by a glucose oxidase method. Diabetes was diagnosed by World Health Organization criteria (11): a plasma glucose level of ≥11.1 mmol/l 2 h

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Abbreviations: dBP, diastolic blood pressure; MBP, mean blood pressure; NIDDK, National Institute of Diabetes and Digestive and Kidney Diseases; PCOS, polycystic ovary syndrome; sBP, systolic blood pressure; SHBG, sex hormone–binding globulin; WHR, waist-to-hip ratio; WTR, waist-to-thigh ratio.

Table 1—*Clinical characteristics of 695 nonpregnant Pima Indian women with or without history of menstrual irregularity*

Age (years)	18–24		25–34		35–44		
Menstrual irregularity	No	Yes	No	Yes	No	Yes	*P* value
n	135	36	235	61	180	48	—
BMI (kg/m²)	33.5 ± 7.7	37.6 ± 9.1	35.7 ± 7.2	39.3 ± 10.2	36.4 ± 7.6	38.9 ± 7.9	<0.0001
Waist (cm)	103.7 ±18.2	114.0 ± 20.6	110.9 ± 18.4	117.1 ± 22.5	114.1 ± 18.6	120.8 ± 18.6	<0.0001
WHR	0.87 ± 0.06	0.90 ± 0.06	0.90 ± 0.09	0.91 ± 0.07	0.92 ± 0.06	0.95 ± 0.05	<0.004
WTR	1.56 ± 0.22	1.64 ± 0.23	1.65 ± 0.26	1.74 ± 0.32	1.72 ± 0.25	1.84 ± 0.20	<0.001
Fasting plasma glucose (mmol/l)	5.3 (4.0, 6.9)	5.8 (4.0, 8.5)	5.8 (4.1, 8.0)	7.1 (4.4, 11.5)	6.7 (4.5, 10.2)	7.2 (4.8, 10.6)	<0.0003
2-h plasma glucose (mmol/l)	6.4 (4.6, 9.0)	7.0 (4.7, 10.4)	7.6 (4.8, 12.0)	9.1 (4.9, 16.9)	9.2 (5.3, 16.2)	10.7 (6.7, 17.2)	<0.002
HbA_{1c} (%)	5.5 ± 1.3	6.3 ± 2.3	6.0 ± 1.8	7.1 ± 2.7	6.9 ± 2.4	7.2 ± 2.2	<0.0002
Menarche (years)	12.3 ± 1.2	11.7 ± 1.1	12.2 ± 1.5	12.4 ± 1.3	12.2 ± 1.6	12.0 ± 1.6	NS
Gravidity (*n*)	1.2 ± 1.5	1.2 ± 1.5	3.0 ± 2.0	2.1 ± 2.2	3.7 ± 2.4	3.0 ± 2.5	<0.001
MBP (mmHg)	79.4 ± 9.0	83.2 ± 8.6	83.2 ± 9.3	83.8 ± 7.1	86.1 ± 10.2	89.0 ± 9.7	<0.03
Diabetes (%)	5.9	11.1	22.1	34.4	38.3	47.9	<0.014
Ever pregnant (%)	51.1	55.5	88.5	62.3	92.8	83.3	<0.001

Data are means ± SD for normally distributed variables, % for qualitative variables, and geometric means (individual tolerance limit) for the log-normally distributed variables fasting plasma glucose and 2-h plasma glucose. The geometric mean and the individual tolerance limits are the mean ± SD computed on the log-transfomed variable and converted to the original scale of measurement. *P* values are for differences between women with or without menstrual irregularity, controlled for age as a continuous variable, by analysis of covariance in a model including all 695 women.

after the glucose load. BMI, defined as body weight in kilograms divided by the square of height in meters (kg/m²), was used as a measure of obesity. Body fat distribution was estimated by waist circumference, and waist-to-hip (WHR) and waist-to-thigh ratios (WTRs) (12).

Reproductive history

Since April 1992, a standardized reproductive history questionnaire has been used to obtain information about previous pregnancies and menstrual history, including use of oral contraceptives within the previous 12 months. Information about other methods of contraception was not available. Lactation amenorrhea has been infrequent in this population because the women rarely exclusively breastfeed (N. Burton Attico, personal communication). Women may well have had alternate periods of oligomenorrhea and amenorrhea; consequently, our aim was to get information about clinically relevant menstrual irregularities. We, therefore, defined menstrual irregularity as an interval of 3 months or more between menses, when not pregnant, since age 18 years.

Statistical analysis

Analyses were conducted using the natural logarithms of fasting and 2-h plasma glucose to reduce skewness. Age-adjusted means between women with menstrual irregularity and women with regular periods were compared using analysis of covariance. We compared prevalence of diabetes between groups using χ^2 test statistics; the Mantel-Haenszel procedure was used to control for potential confounders. In addition, the association between type 2 diabetes and menstrual irregularity was assessed with multiple logistic regression analysis to control for potential confounders.

RESULTS — The prevalence of history of menstrual irregularity was 21% (145/695). Type 2 diabetes prevalence was 33% in 145 women with history of menstrual irregularity, in contrast with 24% in 550 women with regular menses ($P < 0.05$). Mean BMI was 36.1 kg/m² (range 18.1–63.7). All but 80 of the 695 participants were obese (BMI ≥27 kg/m²). In the 145 women with a history of menstrual irregularity, age-adjusted mean BMI was 38.7 kg/m², significantly higher than in the 550 women with regular menses (35.4 kg/m², $P < 0.05$). Current oral contraceptive use was 8.1%, with no significant difference between groups (6.9 and 8.4%, respectively, $P = 0.57$, controlled for age).

Characterization of the study population by age-group and history of menstrual irregularity is shown in Table 1. The age of menarche was similar in all groups. However, in age-adjusted analysis, women with a history of menstrual irregularity had significantly higher ($P < 0.05$) BMI, waist circumference, WHR, WTR, 2-h plasma glucose, HbA_{1c}, MBP, and prevalence of type 2 diabetes, as well as decreased gravidity.

Controlled for age, but not obesity, diabetes was significantly associated with history of menstrual irregularity (odds ratio = 1.6; 95% CI = 1.1–2.5), but not with nulligravidity (odds ratio = 1.2; 95% CI = 0.7–1.9). Controlled for BMI in addition to age, similar results were obtained; while the association between diabetes and history of menstrual irregularity was virtually identical, however, it was no longer quite statistically significant (odds ratio = 1.5, 95% CI = 0.99–2.3). Further control for oral contraceptive use did not substantially change the odds ratio (odds ratio = 1.5, 95% CI = 0.98–2.3), and there was no significant interaction between oral contraceptive use and menstrual irregularity, $P = 0.10$ (i.e., the odds ratio for diabetes and menstrual irregularity did not differ between oral contraceptive users and nonusers). Furthermore, odds ratios were similar in analyses that excluded women who were using oral contraceptives (age-adjusted odds ratio = 1.5).

Age-adjusted prevalence of type 2 diabetes is shown within quartiles of BMI in Fig. 1. Differences in prevalence of diabetes between women with or without history of menstrual irregularity were greatest among the least obese group of women. In the lowest quartile (BMI < 30 kg/m²), women with a history of menstrual irregularity had a significantly higher prevalence of diabetes (37%) than women without a history of menstrual irregularity (13%; age-adjusted odds ratio = 4.2; 95% CI = 1.6–10.8). This difference is less than half as large in the 2nd quartile. In the 3rd and 4th quartiles of BMI, diabetes occurred at a high rate regardless of menstrual history.

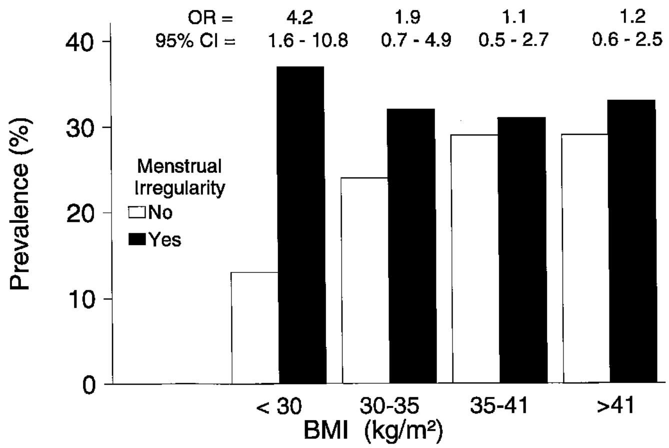

Figure 1—*Age-adjusted prevalence of type 2 diabetes stratified by quartiles of BMI in 695 women with or without menstrual irregularity. OR, odds ratio.*

Adjusted for the effects of age and among the least obese women, those with a history of menstrual irregularity had a significantly higher mean WTR (1.63) than those with regular periods (WTR = 1.49, $P < 0.0013$). Age-adjusted waist girth and WHR did not differ significantly between women with and without history of menstrual irregularity (92.3 and 90.5 cm, $P = 0.38$; 0.89 and 0.87, $P = 0.09$, respectively).

When adjusted for age and BMI within this least obese group of women, history of menstrual irregularity was still significantly associated with a high prevalence of diabetes (odds ratio = 3.5, 95% CI = 1.3–9.5). However, when adjusted for age and WTR, the association between menstrual irregularity and diabetes was less and was no longer statistically significant (odds ratio = 2.5, 95% CI = 0.8–7.6).

CONCLUSIONS — The least obese group of Pima Indian women with a history of menstrual irregularity had a higher prevalence of diabetes than women with regular menses, even when adjusted for the effects of age and overall obesity. At greater degrees of obesity, a strong risk factor for type 2 diabetes (8), there was less difference in diabetes prevalence, such that among women in the upper two BMI quartile groups, diabetes occurred at a high rate regardless of menstrual history.

Charles et al. (1) previously reported an association between nulligravidity and diabetes in a much larger sample of Pima Indian women (age- and obesity-adjusted odds ratio = 2.0; 95% CI = 1.5–2.7); in the present smaller data set, this association was much less pronounced and was not statistically significant. Absence of a significant association between nulligravidity and type 2 diabetes in this data set might be because pregnancy is now more a matter of choice because of contraceptive use. By contrast, in the present study, menstrual irregularity, which is often a consequence of anovulation, was significantly associated with type 2 diabetes.

With or without adjustment for use of oral contraceptives in our analysis, the results of the relationship between menstrual irregularity and diabetes were essentially the same. Furthermore, menstrual irregularity was associated with diabetes whether or not women taking oral contraceptives were included in the analysis. This suggests that oral contraceptive use is unlikely to confound the results.

The present study is cross-sectional, and thus one cannot determine the causal nature of the relationship between menstrual irregularity and type 2 diabetes from these data alone. Menstrual irregularity as defined in the present study may be attributed to several causes, and the available data do not allow us to determine the etiology of menstrual dysfunction in these women. However, given our findings, a reasonable explanation for the association between menstrual irregularity and diabetes might be that they share common risk factors, namely hyperinsulinemia, obesity, and more central distribution of fat (4,5,9). There are several possible mechanisms.

First, increased peripheral conversion of androgens to estrogens in adipose tissue is correlated with obesity (13,14). Higher estrogen concentrations could result in menstrual abnormalities and anovulation by negative feedback at the hypothalamo-pituitary level (9). Thus, a high degree of adiposity could explain the relationship between menstrual irregularity and type 2 diabetes. Yet, in our data, the relationship between menstrual irregularity and diabetes is strongest in women with BMI <30 kg/m^2, and this finding does not favor the hypothesis that obesity is the only link between increased diabetes prevalence and menstrual irregularity.

Second, higher diabetes prevalence among women with a history of menstrual irregularity than in women with regular menses might be explained by an association among insulin resistance, hyperinsulinemia, and hyperandrogenemia. Hyperandrogenemia is associated with oligomenorrhea in insulin-resistant Pima women of child-bearing age (9). Insulin resistance and hyperinsulinemia are common in Pima Indians with type 2 diabetes (12,15). In vitro, insulin can stimulate ovarian production of androgens (16). This mechanism is believed to be involved in the pathogenesis of PCOS (17), a condition associated with a high risk of type 2 diabetes (6) and characterized by insulin resistance, hyperandrogenemia, and menstrual irregularities. In hyperandrogenic women (18) and in women with PCOS (19), only those with anovulation are insulin resistant.

Third, hyperinsulinemia inhibits sex hormone–binding globulin (SHBG) production by the liver (20), and is associated with low SHBG concentrations, which leads to higher free testosterone concentrations (21). Low SHBG concentration is a risk factor for type 2 diabetes in women (22).

In the present study, the relationship between menstrual irregularity and diabetes was limited to the least obese group of women, among whom those with menstrual irregularity had a greater WTR than women with regular menses, suggesting that they may have increased central or visceral adiposity (23,24). Estimates of body fat distribution, such as waist circumference and WTR, may be as useful as more complicated measures for identifying groups of individuals whose body habitus puts them at high risk of developing type 2 diabetes (24). That the relationship between menstrual irregularity and type 2 diabetes was no longer significant when WTR was included in a multivariate model suggests that the effect of menstrual irregularity is mediated through its relation to visceral adiposity. Insulin resistance and visceral adiposity are highly correlated (23). Visceral adiposity is associated with aberrations in steroid hormone secretion such as hyperandrogenemia (25–27). Thus, the greater WTR found in Pima women with irregular menses suggests that these women have both hyperinsulinemia and hyperandrogenemia and that these anomalies are involved in the dysregulation of the menstrual cycle.

To our knowledge, no other population-based studies have examined the relationship between menstrual irregularity and diabetes. Given the increasing prevalence of type 2 diabetes in other ethnic groups with risk factors similar to those of the Pimas, we would expect to see a similar relationship with menstrual irregularity. Further research that includes data on the etiology of the menstrual irregularity, thereby allowing a more precise definition, might shed light on the mechanisms of this association.

In conclusion, we found a strong association between history of menstrual irregularity and increased diabetes prevalence in the least obese group of Pima Indian women, consistent with the previously reported relationship between menstrual irregularity and insulin resistance (9). High BMI confers a high risk of type 2 diabetes, regardless of menstrual history. The findings reinforce the need to evaluate women with menstrual irregularity for hyperglycemia.

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