Incidence of diabetes mellitus in women following impaired glucose tolerance in pregnancy is lower than following impaired glucose tolerance in the non-pregnant state

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Summary Impaired glucose tolerance (IGT), which is asymptomatic and requires a glucose tolerance test for detection, is a well-known risk factor for diabetes mellitus. Outside the research setting it is rarely identified in people who lack specific risk factors for diabetes except during pregnancy, at which time screening with an oral glucose challenge is a routine procedure. A 75-g oral glucose tolerance test was performed during the latter part of pregnancy or during a routine epidemiology survey in 15–39-year-old Pima Indian women with no history of abnormal glucose tolerance. Those with IGT by World Health Organization criteria were included in this study. Diabetes incidence in women was compared between those whose IGT was first detected during pregnancy and those who were not pregnant when IGT was first recognized. Seventeen of 73 pregnant women and 114 of

244 non-pregnant women developed diabetes within 10 years. When controlled for plasma glucose concentration, age, body mass index, parity and duration of follow-up, those who were not pregnant were at higher risk of developing diabetes than those who were pregnant (hazard rate ratio = 1.71, 95 % confidence interval = 1.01–2.91). Previous studies had reported that women with IGT during pregnancy are at higher risk of diabetes than women with normal glucose tolerance. This study suggests that women with IGT during pregnancy are at lower risk than non-pregnant women with a similar plasma glucose concentration who, in the clinical setting, are likely to remain unrecognized. [Diabetologia (1996) 39: 1334–1337]

Keywords Diabetes mellitus incidence, impaired glucose tolerance, pregnancy.

Gestational diabetes mellitus or abnormal glucose tolerance during pregnancy has been recognized for many years as a risk factor for the future development of diabetes [1–6]. The risk of diabetes is higher in women who are older [2], are more obese [2, 4, 7–9], or have a more severe abnormality of glucose tolerance during the pregnancy [2, 3, 6, 7, 9]. Greater parity has been associated with diabetes in some [5, 8], but not all studies [9–11]. Among non-pregnant adults, impaired glucose tolerance (IGT) is also a risk factor for subsequent diabetes [12–15]. However,

in the absence of pregnancy, glucose tolerance tests are rarely performed in young asymptomatic people as they are during pregnancy, which is a state known to affect glucose tolerance [16–18]. The comparative risks of diabetes following IGT first recognized in pregnant and non-pregnant women are therefore unknown but may be of prognostic importance. The purpose of this study is to compare the incidence of diabetes within 10 years following the recognition of IGT in women who were and in those who were not pregnant when IGT was first recognized.

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Abbreviations: IGT, Impaired glucose tolerance; NIDDM, non-insulin-dependent diabetes mellitus.

Subjects and methods

Since 1965, Pima Indians living in the Gila River Indian Community in southern Arizona, a population with very high rates of non-insulin-dependent diabetes mellitus (NIDDM) [19] have participated in a longitudinal study of diabetes [14, 20].

Table 1. Characteristics of women at time of recognition of IGT, duration of follow-up, parity at end of follow-up, and new cases of NIDDM

Recognition	Pregnant at time of recognition of IGT			
	No (<i>n</i> = 244)		Yes (<i>n</i> = 73)	
Age (years)	29.2 ± 5.7	15.3–39.2	26.0 ± 5.7	15.7–39.9
2-h plasma glucose (mmol/l)	8.8 ± 0.9	7.8–11.0	8.6 ± 0.7	7.8–10.7
Body mass index (kg/m ²)	35.5 ± 6.8	20.9–57.2	33.4 ± 6.3	23.1–50.4
Number of pregnancies	3.4 ± 2.4	1–12	2.5 ^a ± 1.7	1–8
Follow-up				
Years of follow-up	5.1 ± 2.7	0.5–10.0	5.2 ± 2.6	0.8–9.9
Parity at follow-up	3.8 ± 2.5	1–13	4.2 ± 2.2	1–11
New cases of NIDDM	114		17	

Data are mean ± SD and range

^a Includes current pregnancy

Oral glucose tolerance tests (75 g) are performed on women during the latter part of each pregnancy and, approximately every 2 years, on all residents of the Gila River Indian Community over the age of 5 years, regardless of whether or not they are pregnant. World Health Organization criteria [21] were used to diagnose NIDDM (2 h post-load plasma glucose level ≥ 11.1 mmol/l) and IGT (2-h post-load plasma glucose ≥ 7.8 mmol/l and < 11.1 mmol/l). The body mass index (BMI, weight divided by the square of height in kg/m²), measured at the time of first recognition of IGT for non-pregnant women or at the first examination post pregnancy following the recognition for pregnant women, was used as a measure of obesity.

The subjects included in this study were women of at least half Pima and Tohono O'odham heritage who had IGT that was first recognized at age 15–39 years either during a pregnancy or in the non-pregnant state after at least one pregnancy, and who subsequently had at least 6 months of follow-up. Women were followed-up for up to 10 years from the first recognition of IGT – those entering the study after 1985 were followed-up for less than 10 years. The end of the follow-up period was the date of diagnosis of NIDDM or, for those not developing NIDDM within 10 years, the last non-pregnant 2-yearly examination within the 10-year period.

Statistical analysis

A proportional hazards regression model [22] was used to assess the influence of pregnancy at the time of recognition of IGT on the subsequent incidence of NIDDM. This analysis, which controls for potentially confounding variables and uses time preceding development of NIDDM as the outcome variable, accounts for the different lengths of follow-up. Parity was treated as a time-dependent variable in this model and thus increased with time in some women.

Results

Table 1 presents characteristics of the women at the time of recognition of IGT. The 244 women with IGT first identified when they were not pregnant were, on average, older, had higher plasma glucose levels, had a higher BMI, and had been pregnant more times than the 73 women whose IGT was first recognized during pregnancy (*p* < 0.05 for each). Duration of follow-up and parity at follow-up were similar in the two groups.

Table 2. Univariate predictors of NIDDM in women with IGT

	Hazard* rate ratio	95 % CI	<i>p</i> -value
Age (per 5 years)	1.26	1.08–1.48	0.004
2-h plasma glucose (per mmol/l)	1.68	1.41–2.01	< 0.001
Body mass index (per 2 kg/m ²) ^a	1.05	1.00–1.10	0.035
Parity (per pregnancy) ^b	1.14	1.07–1.22	< 0.001
Not pregnant ^c	2.04	1.23–3.40	0.006

* Hazard rate ratios and 95 % confidence intervals (CI) calculated from proportional hazards models. Dependent variable is NIDDM measured when not pregnant;

^a measured when not pregnant

^b Time-dependent variable changed during follow-up

^c At recognition of IGT

Table 3. Multivariate proportional hazards model in women with IGT

	Hazard* rate ratios	95 % CI	<i>p</i> -value
Age (per 5 years)	0.97	0.80–1.18	NS
2-h plasma glucose (per mmol/l)	1.59	1.33–1.89	< 0.001
Body mass index (per 2 kg/m ²) ^a	1.04	0.99–1.10	NS
Parity (per pregnancy) ^b	1.14	1.05–1.24	0.002
Not pregnant ^c	1.71	1.01–2.91	0.048

* Hazard rate ratios and 95 % confidence intervals (CI) calculated from the model. Dependent variable is NIDDM measured when not pregnant;

^a measured when not pregnant

^b Time-dependent variable changed during follow-up;

^c At recognition of IGT

During 0.5–10.0 years of follow-up, NIDDM developed in 17 (23.2 %) women with IGT first recognized during pregnancy and in 114 (46.7 %) women with IGT while not pregnant ($\chi^2 = 12.7, p < 0.001$), but these rates may be confounded by the variables listed above.

On univariate analyses, age, plasma glucose level, BMI, parity and whether or not the woman was pregnant at time of recognition of IGT were each significantly associated with subsequent NIDDM (Table 2). On multivariate proportional hazards analysis, plasma glucose level, parity, and pregnancy at the time

Fig. 1. Incidence of NIDDM in women who were (lower line) and those who were not (upper line) pregnant at time of the first recognition of IGT, adjusted by proportional hazards regression to the mean age (25 years), 2-h post-load glucose (8.5 mmol/l) and BMI (35 kg/m²) at IGT recognition and the mean of the average parity during follow-up (3.5 pregnancies)

of recognition of IGT were all significantly and independently associated with subsequent NIDDM (Table 3).

Figure 1 shows the cumulative incidence of NIDDM in the women who were and were not pregnant at the time they had IGT, adjusted by proportional hazards regression to the mean age and plasma glucose level at the time, non-pregnant BMI at or following IGT and average parity during follow-up. Those who were not pregnant when IGT was first found were more likely to develop NIDDM than those who were pregnant (Table 3).

Discussion

IGT conferred a higher risk of subsequent diabetes when identified in non-pregnant women than when identified during pregnancy. No symptoms or other risk factors for diabetes, other than Pima Indian heritage, and either residence in the Gila River Indian Community or being in receipt of prenatal health care at the Community hospital, were used as criteria to select subjects for oral glucose tolerance tests. Thus, neither group was selected because of suspicion of high glucose levels. Some studies have shown that risk of diabetes increases with increasing parity [5, 8], but this was not found in a previous study in this population [11]. However, in the present study, the number of pregnancies used as a time-dependent variable that was incremented as subjects had pregnancies was significantly associated with the subsequent development of diabetes, and this variable was used in the multivariate proportional hazards

analysis. The present analyses were limited to women who were pregnant at time of entry in the study, or who had previously had at least one pregnancy, because in this population, women who have never been pregnant are at a particularly high risk of diabetes [11]. This analysis does not exclude women with a history of menstrual irregularity, a condition also associated with higher plasma glucose levels and which increases risk of NIDDM in this population [23]. These women may have been less fertile and therefore more likely to be seen in the clinic when not pregnant than women with regular menstrual cycles.

Previous studies in this population have found abnormal glucose tolerance, in both pregnant [3] and non-pregnant [12–14] adults, to be a risk factor for subsequent NIDDM, and similar results have been found in other populations, as reviewed by Tuomilehto et al. [24]. However, unlike other studies, this study has compared the relative risk in pregnant and non-pregnant women. Systematic oral glucose tolerance tests in non-pregnant as well as pregnant women in this population have made this comparison possible. There is no reason to suspect that the findings presented in this paper would not be found in other populations, but the studies as yet have not been done.

Harris [25] has suggested that most gestational diabetes represents a pre-existing abnormality of glucose tolerance identified only because of the pregnancy, and it could be argued that this may also be the case for IGT. If so, rates of subsequent NIDDM would not be expected to differ between those who were and those who were not pregnant, and this was not the case. A likely explanation for the present findings is that women at highest risk of NIDDM developed IGT even in the absence of pregnancy while those at lower risk had normal glucose tolerance until subjected to the stress of pregnancy. This concept was expressed by Jackson [26] over 30 years ago. He stated that he did not subscribe to the idea that pregnancy was 'diabetogenic' in women with basically normal metabolism, but rather uncovered a latent or prediabetic state in these 'normal' women. This suggests that being pregnant would neither increase nor decrease the risk of NIDDM following IGT, but that the group with IGT identified during pregnancy includes women with a less severe abnormality for a given glucose, age and BMI. Since IGT is generally asymptomatic, it would remain unrecognized in the usual clinical setting where glucose tolerance tests are not routine. The predictive value of the glucose tolerance test in non-pregnant women was reported by Kjos et al. [27] who tested women in the postpartum period. Although their data are limited to women whose abnormal glucose tolerance was first identified during pregnancy, those women who also had abnormal glucose tolerance after pregnancy were at a significantly higher risk of developing diabetes within 5 years

than were the women whose abnormality was confined to the pregnancy.

While pregnant women with abnormal glucose tolerance are more likely to develop diabetes than pregnant women with normal glucose tolerance [3], in this study they were less likely to develop diabetes than non-pregnant women with a similar degree of abnormal glucose tolerance. This may be because pregnancy is self-limited while the cause of IGT in non-pregnant women persists, or because the increased risk of subsequent diabetes associated with IGT during pregnancy is revealed by, but not caused by, the pregnancy. This may have important clinical implications as techniques in diabetes prevention are developed. Women whose IGT is identified only during pregnancy may have milder abnormalities that are less likely to progress to diabetes within 10 years, while most of the women at the greatest risk of progressing to diabetes after developing IGT are likely to remain unidentified.

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