

Prediabetes and Perinatal Mortality

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OBJECTIVE — The association between gestational diabetes mellitus (GDM) and perinatal outcome is largely based on case series and retrospective studies that found an increased risk of perinatal mortality and stillbirth as the onset of diabetes approached. Our objective was to assess the relationship between latency to diabetes and perinatal outcome of prediabetic pregnancies in a contemporary population of women with adult-onset diabetes.

RESEARCH DESIGN AND METHODS — A population of 403 diabetic women from two recruitment sites completed a pretested questionnaire.

RESULTS — Details of 1,181 pregnancy outcomes were obtained. This comprised 1,024 live births, 22 stillbirths, and 8 early neonatal deaths. Crude analysis suggested a relationship between time to diabetes (latency) ≤ 20 years and both perinatal death and stillbirth: odds ratio (95% CI), 2.41 (1.17–4.95) and 2.15 (0.93–4.98). Generalized additive modeling revealed a nonlinear relationship between the variables time to diabetes, and maternal age and perinatal outcome. Final logistic regression analysis was then performed for the outcomes perinatal death and stillbirth, with maternal age as a second-degree polynomial, year of birth as a continuous variable, and time to diabetes dichotomized ≤ 20 years to diagnosis and > 20 years. This final analysis documented a significant association between time to diabetes ≤ 20 years and both perinatal death (4.06 [1.79–9.36]) and stillbirth (3.35 [1.25–9.05]).

CONCLUSIONS — There appeared to be an increased risk of perinatal death and stillbirth in pregnancies occurring in the last 20 years before the diagnosis of diabetes.

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The concept of prediabetes arose in the 1950s with the publication of a number of case series and retrospective cohort studies that examined the reproductive outcomes of diabetic women in the years before they were diagnosed with diabetes (1–6). The majority of these studies concluded that the perinatal mortality rate was increased in these prediabetic pregnancies and that this rate increased steadily until the time of diagnosis of diabetes. This condition of “prediabetes” later became known as gestational diabetes mellitus (GDM), and tests such as the glucose tolerance test were devised to diagnose it (7–9). Unfortunately, the association between GDM and perinatal

outcome remains controversial, due in part to a paucity of well-designed cohort studies and clinical trials (10,11). Our study proposed to reexamine the association between prediabetes and perinatal mortality in a more contemporary population of diabetic women who delivered before screening for GDM in pregnancy became widespread.

RESEARCH DESIGN AND METHODS

From March 1997 to March 1998, women with adult-onset diabetes were recruited from the Calgary Regional Health Authority Diabetes Clinic and the office of one of the authors (S.R.). The subjects completed a self-administered

pretested questionnaire detailing their diabetic and reproductive histories. Stillbirth was defined as death in utero after 20 weeks' gestation and perinatal death as all stillbirths and neonatal deaths in the first week of life (early neonatal death). The completed questionnaires were reviewed with the subjects by the center staff or one of the investigators (S.L.W.). To limit self-selection bias, questionnaires were provided only after a registration card had been completed and before the subjects appreciated the reproductive history content of the questionnaire. This was to monitor for the possibility that women with adverse reproductive histories would decline to participate to avoid having to recall painful life events. After crude analysis, further analysis was performed with generalized additive models to explore the functional form of the relationship between the variables and the adverse pregnancy outcomes. This was followed by multiple logistic regression modeling with appropriate transformations as suggested by the preceding analysis.

Generalized additive modeling (GAM) is a relatively new statistical technique that allows investigation of nonlinear relationships between variables and outcomes (12–14). Instead of arbitrarily forcing variables into a linear relationship with outcomes, as in logistic regression, the relationship between a variable and the outcome is estimated nonparametrically using smoothing operations. Graphical displays can then be created to visualize the relationship between the variable and the outcome. Partial likelihood tests are also available to determine whether the smoothed function is significantly different from a linear function.

RESULTS — Over the 12-month period, 403 women were recruited. Five questionnaires could not be accounted for, but three of these subjects were reached by phone, and all three denied any previous perinatal deaths. The average age of the subjects was 60 years, and the average age of diagnosis of diabetes was 54 years. The cohort was made up mainly of newly diagnosed diabetic patients. Of the 403 women, 59 had never been pregnant, and 1 had all her pregnancies after the diagnosis of diabetes. This left 343 women, who reported 1,054

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Abbreviations: GAM, generalized additive modeling; GDM, gestational diabetes mellitus.

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

Table 1—Association between time to diabetes of <20 years and perinatal death

Time to diabetes	Perinatal death	No perinatal death	Stillbirth	Live birth	Total
≤20 years to diabetes	13 (5.0)	247	9 (3.5)	251	260
>20 years to diabetes	17 (2.1)	777	13 (1.6)	781	794
Total	30	1,024	22	1,032	1,054

Data are n (%) or n. Perinatal death: risk ratio (95% CI), 2.34 (1.15–4.74); odds ratio (95% CI), 2.41 (1.17–4.95); two-sided Fisher's exact, $P = 0.0288$. Stillbirth: risk ratio (95% CI), 2.11 (0.91–4.89); odds ratio (95% CI), 2.15 (0.93–4.98); two-sided Fisher's exact, $P = 0.0826$.

prediabetic pregnancies, not including miscarriages. Of these women, 24 (7%) reported being diagnosed with GDM during pregnancy, 7 (29%) of whom recalled being treated with insulin. The 1,054 reported pregnancies comprised 1,024 live births, 22 stillbirths, and 8 early neonatal deaths.

The explanatory variables considered in analysis were time from pregnancy to the onset of diabetes (time to diabetes), maternal age, and year of birth. For the crude analysis, the interval between pregnancy and the diagnosis of diabetes (time to diabetes) was dichotomized at 20 years. This cutoff was chosen both intuitively and because it represented the 75th percentile of this variable. Crude analysis suggested a relationship between time to diabetes ≤20 years and both stillbirth and perinatal death (Table 1). Further analysis was performed with multiple logistic regression, and an unexpected interaction was found between maternal age and time to diabetes when the variables were in continuous form, but not when they were dichotomized. This suggested the possibility of nonlinear relationships between the log odds of our outcomes, perinatal death and stillbirth, and the explanatory variables. GAM suggested an increased risk of perinatal death at the extremes of maternal age and a gradual increase in risk in the last 20 years before the diagnosis of diabetes (Fig. 1). The graph for the out-

come stillbirth was identical to that for perinatal death (not shown). The graph displays the relationship between each variable and the smoothed function calculated for each variable, allowing inferences to be made as to the functional form of the relationship between the variable and the log odds of the outcome (13,14). Based on these results, a final model was fit with maternal age transformed into a second-degree polynomial, time to diabetes dichotomized at 20 years, and year of birth untransformed. This analysis suggested an increased risk of both stillbirth (odds ratio [95% CI], 3.35 [1.25–9.05]) and perinatal death (4.06 [1.79–9.36]) in the last 20 years prior to diagnosis of diabetes (Table 2). The analysis was repeated, excluding the patients in whom GDM had been detected. The point estimates and significance tests were not significantly different whether or not these patients were included (data not shown). The final analysis was repeated again with robust regression to allow relaxation of the assumption of independence within families, and this did not increase the P values (data not shown). Data from a large perinatal database (Alberta Medical Association Reproductive Care Committee, Edmonton, Alberta, Canada), with data on all perinatal deaths in Alberta from 1955 to 1995, were available to cross-reference with our subjects' recalled outcomes. In our population, only 12 perinatal deaths occurred in

Alberta during this period, and records confirming early neonatal death or stillbirth were found for 11 subjects. One stillbirth could not be confirmed.

CONCLUSIONS— The intent of our study was to investigate a possible association between the prediabetic period and perinatal mortality because prediabetes is directly related to GDM. In both the crude and adjusted analyses, the recalled rates of perinatal mortality and stillbirth increased as the diagnosis of diabetes approached. Of course, as in all observational studies, our findings are vulnerable to bias. The most serious possible bias is misclassification of perinatal outcomes by the subjects. This would only affect the results if the bias occurred differentially. This may have occurred because women who had pregnancies in the last 20 years before the diagnosis of diabetes also had their pregnancies more chronologically recently compared with women with longer latency periods. The majority of our patients were recently diagnosed with diabetes: if recall of perinatal outcomes is more accurate for recent versus distant events, this could account for our results. However, our validity check suggested good agreement between recalled adverse perinatal events and our perinatal database, with 91% agreement. Furthermore, the rate of perinatal death was higher, as expected, in the pregnancies that were chronologically more remote (Fig. 1).

The accuracy of estimating the time of onset of diabetes is likely to be poor. However, this misclassification would be non-differential and would bias the results toward a null finding. Therefore, this would make it more difficult to detect an association between perinatal outcome and latency to diabetes and would not account for our findings. The finding of increased perinatal mortality in diabetic women in the years most immediate to

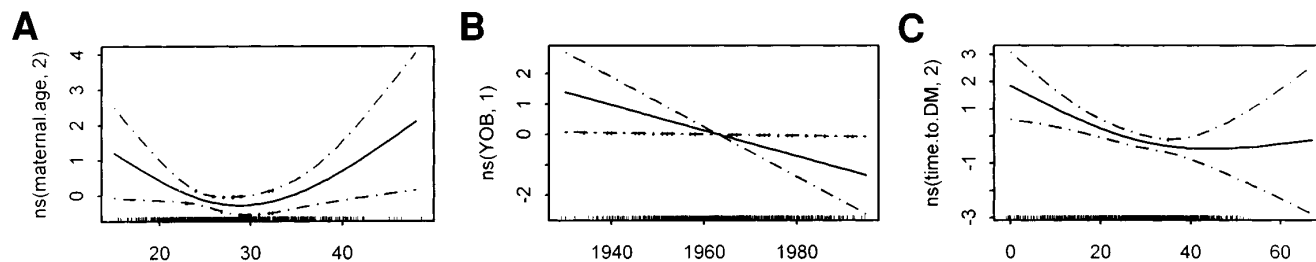


Figure 1—Parametric smoothed functions for maternal age (A), year of birth (B), and time to diabetes (C) for the outcome perinatal death. The y axis indicates the nonparametric estimates of the log odds ratios.

Table 2—Definitive logistic regression models for the outcomes perinatal death and stillbirth

Outcome	Coefficient (β_4)	Odds ratio	P
Perinatal death	1.4	4.06	0.0017
Stillbirth	1.21	3.35	0.022

Coefficients, odds ratios, and P values are for time to diabetes ≤ 20 vs. >20 years. Coefficient values are based on the equation $\beta_0 + \beta_1(\text{maternal})^2 + \beta_2\text{maternal} + \beta_3\text{YOB} + \beta_4\text{latent with latent, time to diabetes } \leq 20$ vs. >20 years; maternal, maternal age; YOB, year of birth.

their diagnosis could also be explained by the fact that they were already frankly diabetic and not appropriately managed during their pregnancies. This is plausible, and there is some data suggesting that diabetes typically develops 4–7 years prior to diagnosis (15). However, it seems unlikely that this could explain the increased rate of perinatal losses, even in the 10–20 years prior to diagnosis.

There are several potential explanations for an increased risk of perinatal death with decreasing latency to overt diabetes. Based on available evidence, it is clear that subjects who eventually succumb to adult-onset diabetes are insulin-resistant for up to 40 years before diagnosis (16–18). This insulin resistance, coupled with the added burden of pregnancy, leads, in some subjects, to the inability of pancreatic β -cells to maintain glucose homeostasis, and ultimately to hyperglycemia (19). Hyperglycemia is a likely culprit, since it has been generally regarded as the cause of perinatal loss in pregnancies in type 1 diabetic patients. However, there are other conditions that may coexist with insulin resistance, such as hypertension and macrovascular disease, and that could also be associated with perinatal loss (20–22). Therefore, it is not certain that the increased risk of perinatal loss in these pregnancies would have been reduced by identification and treatment of GDM, had it occurred.

GDM remains a controversial subject, due in part to a paucity of studies clearly establishing an association with perinatal outcome. Unfortunately, screening for and treatment of GDM has become the standard of care, making further study difficult. In

addition, sample size estimates for randomized controlled trials to determine whether screening and treatment reduce perinatal mortality or macrosomia are prohibitively large (23). Thus, for the foreseeable future, it may be that evaluating the association between perinatal mortality and GDM may only be possible through indirect approaches such as that presented here.

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