Diabetes and Abnormal Glucose Tolerance in Women With Previous Gestational Diabetes

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OBJECTIVE — In Spanish women with gestational diabetes mellitus (GDM), we aimed to study the progression to diabetes and abnormal glucose tolerance (AGT) and identify predictive factors.

RESEARCH DESIGN AND METHODS — In 696 women with GDM and 70 control women, glucose tolerance was evaluated postpartum and at 5-year intervals.

RESULTS — In the GDM group, the cumulative risk for diabetes and AGT was 13.8 and 42.4% after 11 years compared with 0 and 2.8% in control women, respectively (P < 0.05). Independent predictive factors for diabetes were previous hyperglycemia, four abnormal glucose values on the diagnostic oral glucose tolerance test (OGTT) or overt diabetes during pregnancy, 2-h blood glucose on the diagnostic OGTT ≥ 11.7 mmol/l, gestational age at diagnosis < 24 weeks, and prepregnancy BMI ≥ 26.4 kg/m². All of these factors (some with different cutoff points) in addition to fasting glycaemia were predictors of AGT also. The risk was nonlinear. Four abnormal glucose values on the diagnostic OGTT or overt diabetes during pregnancy was the strongest predictive factor for diabetes (relative risk 3.92), and prepregnancy BMI was the predictive factor with the highest attributable fraction in the whole group (13.3%). When first postpartum OGTT data were included in the analysis, predictors changed, but the overall prediction was similar.

CONCLUSIONS — Spanish women with GDM have an increased risk of diabetes and AGT. Predictive factors display a nonlinear relationship. The strongest predictive factor for diabetes was four abnormal glucose values on the diagnostic OGTT or overt diabetes during pregnancy; the factor with the highest attributable fraction in the whole group was prepregnancy BMI.

In this study, our objective was to assess the progression to diabetes and abnormal glucose tolerance (AGT) of Spanish women with GDM who attended our hospital and to identify predictive factors.

RESEARCH DESIGN AND METHODS

Patients and protocol

Of the 982 women diagnosed with GDM between 1986 and 1993 who attended the Diabetes and Pregnancy Clinic at the Hospital de Sant Pau de Barcelona, 696 returned postpartum for metabolic testing. Screening for GDM with the 50-g, 1-h glucose challenge test was scheduled in all pregnant women in the first visit, and women not diagnosed with GDM repeated the challenge at 24–28 and 31–34 weeks. Criteria for screening and glucose tolerance testing were those enunciated by the Second and Third Workshop-Conferences on Gestational Diabetes (14,15). The treatment protocol for women found to have GDM has been previously described (16).

A subset of 500 women who delivered in the center from January 1987 to December 1993 and had a normal screening test or oral glucose tolerance test (OGTT) in the third screening period were invited to participate as control subjects; 70 of them accepted.

In women with GDM, a 75-g OGTT was performed 6 weeks after delivery or upon cessation of breast-feeding, whichever occurred last. The second test was scheduled 5 years after the first one. No other regular assessment of diabetes was done, but in patients presenting with overt diabetes (17), the event was entered into the study at the moment it occurred. When a woman had GDM in subsequent pregnancies, only the first pregnancy was included in the analysis and the postpartum OGTTs of subsequent pregnancies were considered as part of the follow-up of the first one. Control women initiated follow-up 5 years after delivery. Results were evaluated according to World.
Health Organization (WHO) 1998 criteria (18). When OGTT was diagnostic of diabetes, an additional test was scheduled to confirm the diagnosis, but the first one was used for the calculation of cumulative incidence. We analyzed the progression to diabetes and AGT (diabetes, IGT, impaired fasting glucose [IFG]) and the predictors of progression. Clinical criteria were used to differentiate between type 1 and type 2 diabetes, and C-peptide/insulin measurements were used for confirmation (17).

Antepartum variables considered as potentially predictive were family history of diabetes and previous hyperglycemia—GDM, IGT, or nondiagnostic hyperglycemia (fasting plasma glucose ≥110 mg/dl and <140 mg/dl, in accordance with WHO 1985 criteria applicable at the time the patients attended [17])—age, prepregnancy BMI, previous pregnancies, history of poor obstetric outcome, diagnosis of GDM (gestational age, blood glucose [BG] values, area under the curve [AUC], number of abnormal glucose values, or overt diabetes during pregnancy), GHb, and autoantibody positivity after diagnosis (islet cell antibodies [ICAs], GAD, and tyrosine phosphatase [IA2] antibodies), requirement of insulin therapy, macrosomia (birth weight ≥4,000 g), and spontaneous preterm delivery (<37 weeks). Analyzed postpartum variables included additional pregnancies, additional diagnosis of GDM, BMI, and BMI increment at follow-up. In a subsequent analysis, first postpartum OGTT data (BG and AUC) were also included.

Laboratory analysis
A glucose oxidase method (Technicon RA-XT Analyzer; Technicon Instruments, Tarrytown, NY) was used to measure plasma glucose concentration. GHb was measured by high-performance liquid chromatography, and because three different methods were used during the study period, results are expressed as SDs around the mean. ICAs were measured by indirect immunofluorescence after incubating patient sera for 18 h on frozen sections of human pancreas (blood type O) with aprotinin. The cutoff point for positivity was established at ≥5 JDF units. GAD and IA2 antibodies were measured by a radioligand immunoassay using 35S-labeled in vitro–translated recombinant antigen. The threshold for positivity was set at ≥4.2 units for GAD and ≥3.1 units for IA2 antibodies (95th centile of control samples).

Statistical analysis
Statistical analysis was performed with SPSS 10.0 software. Logistic regression analysis was used to compare women who did and did not attend the follow-up examination. Life table analysis was used to calculate the cumulative incidence of diabetes and AGT in women with GDM and control women, and differences between groups were assessed after a log-rank test. A Cox multiple hazard regression analysis was used to examine the relation between potentially predictive variables and the development of diabetes and AGT at follow-up. In continuous variables, the homogeneity of risk was evaluated assessing the risk for each quintile. The only exception was the number of abnormal values in the diagnostic OGTT, which was divided into tertiles. As the risk for diabetes and AGT was not homogeneous throughout tertiles/quintiles, we grouped them according to the visual display of risk (Fig. 1). Multivariate analysis was used to identify independent variables that were significant predictors of diabetes or AGT. Four multivariate analyses were performed, excluding in each step variables with missing values as follows:

- Model 1: All potentially predictive variables included after transforming continuous variables into tertiles and quintiles and further regrouping, as previously described (343 patients)
- Model 2: Model 1, with exclusion of autoantibody positivity (443 patients)
- Model 3: Model 2, with exclusion of GHb (541 patients)

![Figure 1](image-url)
Model 4: Model 3, with exclusion of BMI and its increment at follow-up (660 patients).

Significance was set at \( P = 0.012 \) (Bonferroni correction for model 4 analysis). Statistical power was calculated assuming a unilateral \( \alpha \) of 0.05 and different survival times for the control and study groups, with most analyses yielding powers >70%.

Finally, we assessed the population attributable fraction (AFp; the proportion of excess cases resulting from an exposure in a defined population) and the exposed group attributable fraction (AFe; the equivalent proportion in the exposed group) (19). These were calculated as:

\[
AFe = \frac{RR - 1}{RR} \\
AFp = AFe \times \% \text{ women with the predictor}
\]

where RR is relative risk.

**RESULTS**

**Validity of the cohorts**

**Women with prior GDM.** A logistic regression analysis, with attendance at follow-up as the dependent variable and all potential predictors of AGT as independent ones, identified women with GDM who came for follow-up as more likely to have received insulin during pregnancy (odds ratio [OR] 1.75, 95% CI 1.17–2.58) and less likely to have had a macrosomic baby (OR 0.44, CI 0.2–0.97).

**Control group.** In a logistic regression analysis, with participation in the study as the dependent variable and BG response to 50-g challenge test at 31–34 weeks, maternal age at pregnancy, and newborn macrosomia as independent ones, control women participating in the follow-up study were more likely to have had a higher BG in response to 50-g challenge test (OR 1.4, CI 1.14–1.70).

**Cumulative incidence of diabetes and AGT**

At 6.16 years (0.05–13.73) of follow-up, 44 women had developed diabetes and 130 had developed AGT (44 diabetes, 61 IGT, and 25 IFG). At 11 years of follow-up, the cumulative risk for diabetes was 13.8% in women with prior GDM and 0% in control women (\( P = 0.02 \)), whereas the corresponding rates for AGT were 42.4 and 2.8% (\( P < 0.001 \)) (Fig. 2). Five women presented with type 1 diabetes, which represented 11.4% of all diabetes cases.

Women with prior GDM and control women differed in the rate of GDM in pregnancies after the index pregnancy (65 vs. 0%), age at follow-up (37.5 [21.8–52.9] vs. 40 years [29.1–51.4]), length of follow-up (6.8 [0.1–13.7] vs. 9.6 years [3.5–13.3]), and follow-up OGTT (fasting BG 5 [3.7–13.9], 30-min BG 8.8 [4.4–19.4], 60-min BG 8.3 [3.3–24], 120-min BG 5.7 mmol/l [1.9–30.5], and AUC 22.3 [12.9–63.8] vs. 4.8 [3.8–6.0], 7.6 [4.2–11.5], 6.3 [2.8–12], 5 [2.3–8.5], and 18.5 mmol/l [10.7–29.1], respectively; \( P < 0.001 \)). Rates of family history of diabetes (53.7 vs. 43.9%), subsequent pregnancies (15.1 vs. 20.9%), and BMI at follow-up (24.5 [16.2–40.3] vs. 24.8 [18.3–38.4] kg/m²) were similar.

**Predictors of diabetes**

For diabetes prediction, potentially predictive variables included in the multivariate analysis were previous hyperglycemia; family history of diabetes; history of poor obstetric outcome; gestational BMI, 5th quintile (=26.4 kg/m²) vs. 1st–4th quintiles; gestational age at diagnosis, 1st quintile (<24 weeks) vs. 2nd–5th quin-
Abnormal glucose tolerance in women with GDM

Table 1—Clinical and analytical characteristics of women with prior GDM included as potentially predictive variables of AGT at 6.16 years (0.03–13.73) of follow-up

<table>
<thead>
<tr>
<th>Potentially predictive variables</th>
<th>n (%)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of diabetes (%)</td>
<td>373/695 (53.7)</td>
<td>54/695 (7.8)</td>
</tr>
<tr>
<td>Previous hyperglycemia (%)†</td>
<td>31 (17–44)</td>
<td>23.3 (15.9–37.9)</td>
</tr>
<tr>
<td>Prepregnancy BMI (kg/m²)</td>
<td>446/694 (64.3)</td>
<td>93/694 (13.4)</td>
</tr>
<tr>
<td>Gestational age at diagnosis (weeks)</td>
<td>30 (8–39)</td>
<td>30 (8–39)</td>
</tr>
<tr>
<td>OGTT at diagnosis (mmol/l)</td>
<td>28.3 (23.6–47)</td>
<td>2.03 (1.35–3.02)</td>
</tr>
<tr>
<td>Fasting blood glucose</td>
<td>4.9 (2.8–9)</td>
<td>7.7 (1.8–14.6)</td>
</tr>
<tr>
<td>60-min blood glucose</td>
<td>11.9 (7.7–18.6)</td>
<td>10.3 (4.7–18.6)</td>
</tr>
<tr>
<td>120-min blood glucose</td>
<td>17/691 (2.5)</td>
<td>1.76 (0.98 kg/m²)</td>
</tr>
<tr>
<td>GAD at follow-up (kg/m²)</td>
<td>25/692 (3.6)</td>
<td>75/535 (14%: ICA 14%, GAD 1.5%, IA2 0.2%)</td>
</tr>
<tr>
<td>GAD at follow-up (kg/m²)</td>
<td>17/691 (2.5)</td>
<td>373/695 (53.7)</td>
</tr>
<tr>
<td>Autoantibody positivity (%)</td>
<td>25/692 (3.6)</td>
<td>373/695 (53.7)</td>
</tr>
<tr>
<td>Subsequent pregnancies (%)</td>
<td>105/696 (15.1)</td>
<td>373/695 (53.7)</td>
</tr>
<tr>
<td>Subsequent diagnosis of GDM (%)</td>
<td>69/105 (65)</td>
<td>373/695 (53.7)</td>
</tr>
<tr>
<td>BMI at follow-up (kg/m²)</td>
<td>2.5 (16.2–40.3)</td>
<td>2.5 (16.2–40.3)</td>
</tr>
<tr>
<td>BMI increment at follow-up (kg/m²)</td>
<td>1.52 (3.73 to 12.29)</td>
<td>1.52 (3.73 to 12.29)</td>
</tr>
</tbody>
</table>

Data are n (%) and median (range). †Previous hyperglycemia includes IGT, GDM, or nondiagnostic hyperglycemia; ‡poor obstetric outcomes are macrosomia, hypertension, recurrent miscarriages, unexplained fetal death, hydramnios, major congenital malformations, recurrent urinary infections, or pyelonephritis in previous pregnancies; †GHb was measured at a median gestational age of 33 weeks (11–42); ‡macrosomia: birthweight ≥4,000 g.

diabetes during pregnancy (RR 3.92, CI 1.46–14.81) and the 5th quintile of postpartum OGTT (RR 5.94, CI 1.76–20.08) were the independent predictors (P < 0.001). Afp of all variables was 45.1%.

Risk of type 1 and type 2 diabetes
Independent predictors of type 1 diabetes were four abnormal values at diagnostic OGTT or overt diabetes, gestational age at diagnosis <24 weeks, and AUC on the diagnostic OGTT ≥30.6 (data not shown). Independent predictors of type 2 diabetes were previous hyperglycemia, prepregnancy BMI ≥26.4 kg/m², four abnormal values at diagnostic OGTT or overt diabetes, and AUC on the diagnostic OGITT ≥30.6 (data not shown).

Predictors of AGT
For prediction of AGT and after analyzing the homogeneity of risk prediction in bivariate analysis, potentially predictive variables included in the multivariate analysis were those included for diabetes prediction, some of them with a different cutoff: pregestational BMI (4th–5th quintiles [≥24 kg/m²] vs. 1st–3rd quintiles), gestational age at diagnosis (1st–3rd quintiles [≤32 weeks] vs. 4th–5th quintiles), BMI at follow-up (4th–5th quintiles [≥25.5 kg/m²] vs. 1st–3rd quintiles), and BMI increment (3rd–5th quintiles [≥0.98 kg/m²] vs. 1st–2nd quintiles).

The multivariate model selected for AGT prediction was again model 4. Independent predictors were previous hyperglycemia (RR 1.94, CI 1.19–3.16), four abnormal values on the diagnostic OGTT or overt diabetes (RR 2.15, CI 1.19–3.87), fasting BG ≥5 mmol/l (RR 1.6, CI 1.02–2.51), 2-h BG ≥11.7 mmol/l (RR 2.05, CI 1.36–3.09), gestational age at diagnosis <32 weeks (RR 1.93, CI 1.26–2.93), and prepregnancy BMI ≥24 kg/m² (RR 1.84, CI 1.26–2.68) (P of the model < 0.001).

Af of independent predictors was 48.4% for previous hyperglycemia, 53.4% for four abnormal values on the diagnostic OGTT or overt diabetes, 37.6% for fasting BG ≥5.5 mmol/l, 51.3% for 2-h BG ≥11.7 mmol/l, 48.1% for glucose values and AUC of first postpartum OGTT among potentially predictive variables. Subjects and events were reduced because some women did not have this test, so that 351 women were included in the multivariate analysis; the 5th quintile of prepregnancy BMI (RR 4.64, CI 1.46–14.81) and the 5th quintile of postpartum 1-h OGTT BG (RR 5.94, CI 1.76–20.08) were the independent predictors (P < 0.001). Af of all variables was 45.1%.
for gestational age at diagnosis <32 weeks, and 45.7% for prepregnancy BMI ≥24 kg/m². AFp was 3.4% for previous hyperglycemia, 2.9% for four abnormal values on the diagnostic OGTT or overt diabetes, 8% for fasting BG ≥5.5 mmol/l, 10.8% for 2-h BG level ≥11.7 mmol/l, 27.5% for gestational age at diagnosis <32 weeks, and 18.1% for prepregnancy BMI ≥24 kg/m². Overall AFp was 55.7%.

Repeating the analysis including first postpartum OGTT, 285 women were included, with insulin therapy (RR 3.91, CI 1.17–13.06) and the 5th quintile of postpartum OGTT 2-h BG (RR 2.67, CI 1.22–5.83) being the independent predictors (P = 0.003). AFp of all variables was 63%.

CONCLUSIONS

Risk of diabetes and AGT

The study and control groups were reasonably representative of the original populations: women with GDM with follow-up differed from those without follow-up in the rate of macrosomia and insulin therapy (which, in turn, have not been found to be predictive of AGT or diabetes), and control women undergoing follow-up were slightly shifted toward “less normal” glucose tolerance (higher glycemic response to glucose screening during index pregnancy). We interpreted these findings as indicating that women with prior GDM who received insulin were probably more concerned about their risk of diabetes, but we have no explanation for the negative association with macrosomia. As to the reasons underlying the higher glycemic response to GDM screening in participating control women, we speculate that this could have been attributable to a higher rate of diabetic background in the family.

As expected, the cumulative incidence of diabetes and AGT in the women with previous GDM was higher than in control subjects (13.8% vs. 0% and 42.4% vs. 2.8%, respectively, 11 years after the incident pregnancy). In women of the same geographic area, ages 25–44 years, the prevalence of diabetes and IGT has been reported to be 1.7 and 8.3%, respectively (20), figures in the range of the cumulative incidence of AGT described here for the control group. Nevertheless, the progression rate of women with GDM to diabetes was lower than previously reported (2–5,8,9), but the risk of AGT was in the higher range. Because both IGT and IFG imply a risk of future diabetes (18), we hypothesize that, with longer follow-up, the cumulative incidence of diabetes in these women might approach the rates seen in the literature. Given that the control group initiated follow-up 5 years after delivery, this might have shifted the survival curve to the right, spuriously increasing the difference between them and women with prior GDM. Nevertheless, a bias is impossible for the cumulative incidence of diabetes (0% in the control group) and probably minimal for AGT (2.8% in the control group).

In explanation for the differences between our study and other studies, it should be noted that we have a more comprehensive screening policy in our center: in addition to the usual screening at 24–28 weeks, additional tests are performed at the first visit and at 31–34 weeks. Patients diagnosed after a positive screening in the third period can be assumed to have a more subtle glucose metabolism derangement than those diagnosed earlier. This would mirror the situation described by O’Sullivan and Mahan (21), with the risk of progression to diabetes increasing as the criteria for GDM diagnosis become stricter. Ethnicity could be another reason, as most of our patients were Caucasian and the risk of diabetes is lower in these subjects (22). Finally, we speculate that tight targets of BG control during pregnancy (16) could have helped to preserve β-cell function (23).

Type of diabetes

As to the type of diabetes, these women, when becoming diabetic, essentially developed type 2 diabetes: the cumulative incidence of type 1 diabetes at 11 years was 0.7%, whereas published studies in Caucasian women with GDM have reported figures of 1.7–6.6% in follow-up periods of 2–11 years (8,11–13). This difference could be attributed to the fact that, with one exception (11), these other studies were performed in Northern Europe, where the risk of type 1 diabetes is higher than in Spain (24).

Predictors of diabetes and AGT

As expected, in accordance with previous reports (2,4,5,9), high prepregnancy BMI (surrogate of insulin resistance), severity of GDM (high BG values and early diagnosis), and previous hyperglycemia (both surrogates of inadequate β-cell function for the prevailing insulin resistance) were independent predictors of AGT and diabetes at follow-up. It is important to note that the risk attributed to all quantitative predictors is nonlinear, a fact that has been described (only for some variables) in women with prior GDM (10) and in the general population (25). Moreover, it is important to note that prepregnancy BMI is a predictive factor of glucose tolerance at 26.4 kg/m² (slightly overweight range) in the case of diabetes and 24 kg/m² (normal weight range) in the case of AGT. Surprisingly, insulin therapy and BMI at follow-up were not among the predictors, probably because they were represented by other variables (severity of GDM for insulin therapy, and prepregnancy BMI for BMI at follow-up). Furthermore, additional pregnancies did not increase the risk of future diabetes, a fact that contrasts with the results of Peters et al. (26), who reported that a single pregnancy more than tripled the risk of type 2 diabetes in Hispanic women with previous GDM. This could be because of the higher risk of diabetes in the aforementioned study, meaning that the additional risk of subsequent pregnancies would become more evident. The fact that the Summary of the Fourth Workshop-Conference on Gestational Diabetes acknowledges that the influence of parity on the risk of diabetes is controversial and may vary among ethnic groups (27) highlights the importance of this negative finding.

Even more surprising in our study was the fact that autoantibody positivity was not a predictor of type 1 diabetes. Most study findings concur with this point (8,11–13). In 1996, our group published findings indicating that women with GDM who tested positive for ICAs had a higher prevalence of AGT early after delivery (28). At that time, our feeling was that these women would progress to diabetes (either typical type 1 or latent autoimmune diabetes of the adult [LADA]). However, with longer follow-up, the progression to diabetes and AGT of the antibody-negative cohort has become more pronounced, thus diminishing the differences present shortly after delivery.

In relation to the prediction of future diabetes and AGT, some information about AFp and AFp of diabetes predictors has been reported for the general population (29), but is lacking for women with GDM. We would like to remark on its importance, especially on that of AFp, which indicates the percentage of risk in
the whole group that can be attributed to the risk factor, in contrast to AFp and RR, which only point out the risk in subjects positive for a specific predictor. In our study, four abnormal values on the diagnostic OGTT or overt diabetes had the highest AFp for both diabetes and AGT; therefore, it was the strongest predictor in the group of women who presented with this marker (AFp 74.5%). However, because of its low prevalence in the group (4.7%), it became a poor predictor for the whole group (AFp 4.1%). On the other hand, a prepregnancy BMI ≥26.4 kg/m² and a 2-h BG on the diagnostic OGTT ≥11.7 mmol/l were the best predictors for diabetes in the whole group (AFp 13%), and gestational age at diagnosis <32 weeks was the best predictor for AGT (AFp 27.5%). The underlying reason is that even when these predictive factors do not have the highest RR, they are present in an important proportion of the population (20% for the first two—the highest quintile—and 60% for the last one—the first three quintiles). An additional merit of these predictive factors is that they are known in all women with GDM after diagnosis.

Finally, when the first postpartum OGTT data were included, the predictors differed, but overall prediction was similar (worse for diabetes and better for AGT). We favor the model not including first postpartum OGTT because it permits an earlier identification of women at risk.

In conclusion, Spanish women with GDM have an increased risk of diabetes and AGT. The predictive factors display a nonlinear relationship. The strongest predictive factor for diabetes was four abnormal glucose values on the diagnostic OGTT or overt diabetes during pregnancy, and the predictive factor with the highest AFp was prepregnancy BMI.

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