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ORIGINAL ARTICLE

Predictive factors of developing diabetes mellitus in women with gestational diabetes

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Background. To investigate which factors during gestational diabetes pregnancies correlate with the risk of developing impaired glucose tolerance or diabetes 1 year postpartum and to compare this risk in women with gestational diabetes and women with a normal oral glucose tolerance test during pregnancy.
Methods. Of 315 women with gestational diabetes, defined as a 2-hr blood glucose value of at least 9.0 mmol/l at a 75-g oral glucose tolerance test, who delivered in Lund 1991–99, 229 (73%) performed a new test 1 year postpartum. We compared maternal and fetal factors during pregnancy with the test value at follow up. A control group of 153 women with a 2-hr test value below 7.8 mmol/l during pregnancy were invited to a new test 1 year postpartum and 60 (39%) accepted.
Results. At 1 year follow up, 31% of the women with gestational diabetes but only one of the 60 controls showed pathologic glucose tolerance and one had developed diabetes. The following factors in women with gestational diabetes were identified as predicting impaired glucose tolerance or diabetes at 1 year follow up: maternal age over 40 and – in a multiple regression analysis, independent of each other – a high 2-hr value at oral glucose tolerance test during pregnancy and insulin treatment during pregnancy.
Conclusion. The risk of developing manifest diabetes after gestational diabetes may be high enough to justify a general screening or diagnostic procedure in all pregnant women to identify women with gestational diabetes and a postpartum follow up program for them. This study did not identify any particular factor during pregnancy with enough precision to predict a later progression to diabetes.

Key words: gestational diabetes; follow up; diabetes mellitus; predictive factors; population based

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Numerous studies have shown that women with gestational diabetes mellitus (GDM) have a substantial risk of developing type 2 diabetes later in life. Mestman et al. (1) reported in a Hispanic population that 65% of women with GDM developed diabetes during a 12- to 18-year period postpartum. In his classic studies, O'Sullivan (2–4) found a 36% incidence of diabetes in former GDM women during a 22- to 28-year follow-up period. Dornhorst et al. (5) reported a 6- to 12-year follow-up study. Only 17 of 56 women were normal. Damm et al. (6) reported that 34.4% of women with GDM subsequently developed impaired glucose tolerance (IGT) (17%), or diabetes (17.4%). Coustan et al. (7) found in a 3-year follow-up study that only 11% of GDM women developed abnormal glucose tolerance while another study from North America by Metzger et al. (8) reported that 41% have developed diabetes. The large differences between the study results are probably due

Abbreviations: GDM: gestational diabetes mellitus; IGT: impaired glucose tolerance; OGTT: oral glucose tolerance test; ICA: islet cell antibodies; IAA: insulin autoantibodies; GAD: glutamic acid decarboxylase; SDS: standard deviation scores; OR: odds ratios.

to a heterogeneity, both of the patient population and how the GDM was diagnosed in the index pregnancy. In order to evaluate the background risk, a control group of women with normal glucose tolerance during pregnancy is needed. Comparing GDM women with controls, a few studies have reported the excess incidence of follow-up diabetes in GDM women to be 30% (3), 11% (9), 3% (10) and 17% (6), respectively.

Factors associated with an increased risk of developing type 2 diabetes after GDM have been suggested by several authors: a previous history of GDM (11), high maternal age, and overweight (5,7,8,12), early gestational age at diagnosis of GDM (13,14), a high fasting (6,7,13–15) and 2 hr oral glucose tolerance test (OGTT) glucose value (8,12), a low fasting plasma insulin (8) in the diagnostic OGTT, and insulin treatment during pregnancy (13,15). Peters et al. (16) found an additional pregnancy after the GDM pregnancy to increase the risk for future diabetes development. Postpartum weight gain is another risk factor (5,16). Damm et al. (6) found preterm delivery but also insulin response during OGTT in late pregnancies to be independent predictive factors of diabetes development.

The aim of the present study was to investigate which factors are associated with an increased risk of developing type 2 diabetes after GDM. Data were obtained from a population-based study with a probably complete identification of all cases of GDM.

Materials and methods

In the South of Sweden, 99.5% of all pregnant women attend the free antenatal care (17). In the Lund-Malmö region of this area, all pregnant women are offered a 75-g OGTT at 27–28 weeks of pregnancy. Women with first-degree heredity of diabetes mellitus and those with earlier GDM pregnancies are offered the test also at 10–12 weeks of pregnancy.

In Sweden, we follow the definition stated by the European Association for the Study of Diabetes (18), defining GDM as at least 9 mmol/l as 2-hr values after a 75-g OGTT. One year postpartum, we followed the WHO (19,20) definition of impaired glucose tolerance as a 2-hr capillary blood value after a 75-g OGTT between 7.8 and 11 mmol/l and a value above 11 mmol/l is considered to represent diabetes mellitus. We used Hemocue apparatus from Hemocue AB.

Women with gestational diabetes are closely monitored using blood glucose tests six times daily until delivery. Women with repeated values above 8 mmol/l were insulin treated. One year after delivery, all women were again offered an OGTT.

Two materials were collected

The first material consists of all GDM pregnancies delivered in Lund 1991–99. The data were collected from the antenatal records and the Swedish Medical Birth Registry (21). There were 284 women with 315 pregnancies delivering 321 children (2 pairs of twins and 2 sets of triplets). Among the 315 GDM pregnancies, 279 were identified by OGTT screening and the remaining 36 from clinical suspicion, which was verified by clinical blood glucose monitoring. One year after delivery, OGTT tests were offered to these women. A total of 229 tests were performed of the 315 offered.

The second material (controls) consists of 153 women, randomly selected among all women who delivered in the Lund Hospital during January to June 1998 with an OGTT 2-hr value less than 7.8 mmol/l at diagnosis in pregnancy weeks 25–30. They were invited to a 1-year postpartum OGTT. Sixty of them accepted to perform the test.

The study was approved by the local ethics committee of Lund University and informed consent was given.

The following data were collected for the two materials: prepregnancy weight and height, expected date of delivery, OGTT 2-hr value, date at diagnosis, actual delivery date, weight of the mother at delivery, the estimated fetal weight, the newborn infant's weight and length, and the mother's weight and OGTT 2-hr value at 1 year postpartum. Some of these data are tabulated in Table I.

The following data were secured only for the study group: (a) test results in the third trimester of HbA1c ($n = 295$) and of immunologic predictive markers such as islet cell antibodies (ICA), insulin autoantibodies (IAA) and glutamic acid decarboxylase (GAD) autoantibodies ($n = 156$); (b) Ultrasound scanning measurements of fetal biparietal diameter, abdominal diameter, and femur length ($n = 316$); (c) If insulin treatment was given the date it was started; and (d) At the 1-year follow up, antibodies against GAD, ICA and IAA and if these were positive, C-peptide determination. Tests for antibodies and C-peptide were not begun until in 1996.

Using ultrasound-scanning data, fetal weight was estimated using the formula presented by Persson and Waldner (22), and expressed as standard deviation scores (SDS) from the expected fetal weight. For estimates of deviations in birth weight from the expected birth weight, the reference curves of Marsal et al. (23) were used.

Table I. Some characteristics of women at time of follow up

Maternal age		Parity		Number of infants in birth		Maternal weight, kg		Maternal height	
−20	1	1	75	1	222	30–39	1	140–149	1
20–24	9	2	95	2	7	40–49	6	150–159	43
25–29	79	3	41			50–59	53	160–169	135
30–34	78	4+	18			60–69	72	170–179	49
35–39	48					70–79	46	180–189	1
40–44	12					80–89	23		
45–	2					90–99	12		
						100–109	8		
						110–	8		

Statistics

Some risk factors (maternal age and parity) for an abnormal OGTT 2-hr value at follow up were studied using the Mantel–Haenszel method after suitable stratifications and risks were expressed as odds ratios (OR) with 95% confidence intervals (95% CI).

We correlated each of the above mentioned factors with the 2-hr value of the 1-year follow-up OGTT using Pearson's correlations. In this analysis, each participating woman entered only once. When more than one pregnancy had occurred and a follow up was present for only one, this was used. If follow up was present for both pregnancies, one was chosen randomly by flipping a coin. A multiple linear regression analysis was performed studying two factors that had been statistically significant in the bivariate analysis for the 2-hr blood glucose value in OGTT at follow up.

The simultaneous effect of various factors on the risk of developing IGT or GDM 1 year postpartum was studied with the use of a linear logistic multiple regression analysis.

Results

In the second material (controls), 60 women participated in the follow up. Of the 93 non-participants, eight were pregnant at the time of follow up, one had developed type 2 diabetes, and one had left the country. The remaining 83 refused to participate. They did not differ from the 60 with respect to mean age, parity, prepregnancy weight, pregnancy duration, or infant birth weight (data not shown).

Distributions of 1-year postpartum OGTT 2-hr values in the two materials are seen in Fig. 1. Only one of the 60 controls had IGT. Among the GDM patients, 50 of the 229 (22%) had IGT and 21 had diabetes (9%). The difference is highly significant ($P < 0.001$). The OR for having IGT or GDM in women with previous GDM pregnancies vs. controls is 13.2 (exact 95%CI 3.7–82.3) including the woman among the controls who already had developed a type 2 diabetes at follow up.

Table II shows the ORs for some factors studied. There is an increased risk of having an abnormal OGTT at a maternal age over 40 years.

The estimated mean fetal weight in the GSM material (mainly week 32–34) expressed as SDS of fetal weight was 0.75 ± 0.36 (SEM; $n = 295$, $t = 2.1$, $P = 0.04$). The mean newborn weight, expressed as SDS, was 0.49 ± 0.08 (SEM; $n = 305$, $t = 5.9$, $P < 0.001$). The difference between the mean SDS of the fetal and the newborn weight is not statistically significant ($t = 0.71$, $P = 0.31$).

A number of correlations were made as shown in Table III. There is no correlation between a 2-hr OGTT value (expressed as mmol/l) at 1 year follow up and fetal weight, birth weight, maternal prepregnancy weight or BMI, weight at 1 year follow up, or weight change between prepregnancy weight and weight at follow up. A significant correlation is seen between 2-hr OGTT value at 1 year follow

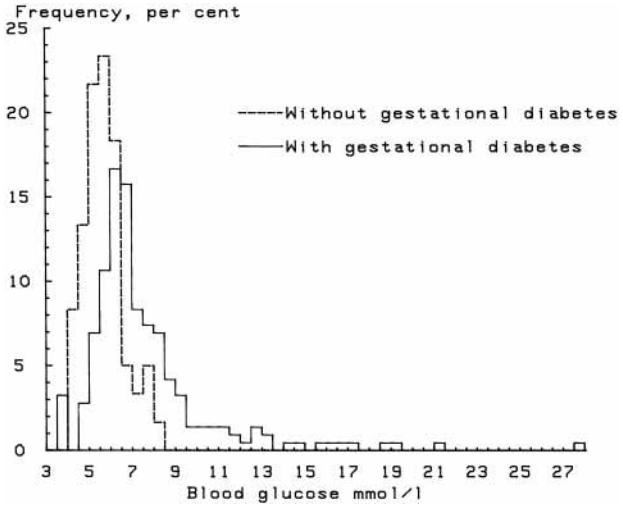

Fig. 1. Frequency distribution of 1-year postpartum 2-hr values at oral glucose tolerance tests in women with and without gestational diabetes.

Table II. Maternal age and parity as risk factors for an abnormal oral glucose tolerance test 2-hr value at 1-year postpartum follow up of women with gestational diabetes. Odds ratios (OR) with 95% confidence intervals (95%CI) stratified for year of delivery and maternal age (for parity) or parity (for maternal age). Each class is compared with all other classes

Risk factor	OR	95%CI	Number of women
Maternal age (years)			
−19	–	–	1
20–24	0.63	0.14–2.76	9
25–29	1.87	0.96–3.65	79
30–34	0.69	0.36–1.33	78
35–39	0.57	0.28–1.16	48
40–44	6.69	1.62–27.6	12
45–	–	–	2
Parity			
1	1.44	0.72–2.85	74
2	0.71	0.39–1.30	95
3	0.77	0.35–1.70	42
4+	2.29	0.66–7.89	17
Unknown	–	–	1

up and OGTT 2-hr value at diagnosis (mmol/l) and also with the value of HbA1c at diagnosis. When the importance of the OGTT 2-hr value at diagnosis and the HbA1c value were tested simultaneously in a multiple regression model, only the former was significant (Table IV).

Women who had insulin treatment during pregnancy had an increased risk for a high 2-hr OGTT value at follow up: 24 among 90 (27%) had 7.8–11.0 mmol/l and 18/90 (20%) had at least 11.1 mmol/l. The corresponding figures for the non-insulin users were 23/132 (17%) and 3/132 (2%), respectively. The time between the date of diagnosis and the date of onset of insulin treatment does not correlate with the follow-up OGTT 2-hr value ($r = -0.04$, $t = 0.53$, $P = 0.35$, $n = 217$).

We performed a linear logistic multiple regression analysis of the risk to have an OGTT value of 7.8 or more at follow up with OGTT during pregnancy, insulin treatment (yes/no), maternal age, parity, and year of delivery as descriptive variables. The OR for an abnormal OGTT at follow up for each unit's increase of OGTT during pregnancy is then 1.29 (95%CI 1.05–1.59) and the corresponding OR for insulin treatment is 3.58 (95%CI 1.91–6.70). The corresponding ORs for the risk of having an OGTT of 11.0 or more at follow up were 1.33 (95%CI 1.04–1.71) for OGTT during pregnancy, and 10.9 (95%CI 3.02–39.5) for insulin treatment. Maternal age does not remain as a significant risk factor in this model.

Table IV. Multiple regression analysis of significance of oral glucose tolerance test (OGTT) glucose value and HbA1c value during pregnancy for OGTT glucose value at follow up

Dependent variable	Regression coefficient	*t*	*P*	Correlation coefficient
OGTT during pregnancy	0.67	4.03	<0.001	0.31
HbA1c during pregnancy	0.04	1.00	0.32	0.17

Antibodies against GAD were identified in 12 among 156 tested women with GDM (7.7%). Eight of them also had ICA antibodies and five IA2A antibodies. Among the 12 women with GAD antibodies, 10 had only been tested at 1-year follow up. One of them had IGT and two had diabetes.

Discussion

In this relatively large population-based study, we confirm the generally accepted fact that GDM women have a substantially increased risk of developing IGT or diabetes 1 year postpartum. Compared with control women (with a 2-hr value below 7.8 mmol/l in a OGTT during pregnancy) the risk is 13.2 times higher in our material or an estimated net excess of 28%. This is in accordance with O'Sullivan (3) who reported 30%, and more than Damm 17% (6), Henry 11% (9) and Persson 3% (10) found.

Ideally, it should be possible to calculate the individual risk of later developing overt diabetes for a woman with GDM. Thus, it is important to

Table III. Correlations between various factors and glucose value in oral glucose tolerance tests (OGTT) at one year follow up of women with gestational diabetes. Each woman counted only once

Descriptive factor	*n*	*r*	*t*	*P*
OGTT 2-hr value at test	204	0.37	5.62	<0.001
HbA1c at diagnosis	196	0.14	2.00	0.02
Prepregnancy weight	209	0.06	0.85	0.20
Prepregnancy BMI	209	0.05	0.68	0.25
Weight at follow up	197	0.08	1.11	0.13
Weight increase to follow up	175	0.13	1.70	0.09
Estimated fetal weight	204	−0.03	−0.41	0.34
Birth weight	222	−0.07	0.96	0.17

Number of individuals (*n*), correlation coefficient (*r*), *t*-tests against $r = 0$ (*t*), and *P*-value are given.

understand the magnitude of risk for different factors in GDM women for future pathologic glucose tolerance. In our study we found the following factors to correlate with abnormal OGTT 1 year postpartum:

1) Maternal age over 40 years which is in accordance with the results by O'Sullivan et al. (12), Dornhorst et al. (5) and Coustan et al. (7). Maternal age disappeared as a risk factor when OGTT value during pregnancy and insulin treatment were added into the model.

2) Two-hour value of diagnostic OGTT which confirms the studies by O'Sullivan et al. (12) and Metzger et al. (8),

3) Insulin treatment during pregnancy which confirms the results from Lam et al. (15) and Catalano et al. (13).

We could not find any correlation between future risk of diabetes development and the following factors: parity, maternal prepregnancy weight, BMI or weight at follow up, HbA1c at diagnosis (when considering the confounding effect of 2-hr value of diagnostic OGTT at diagnosis in a multivariate analysis), intrauterine fetal weight at 32–35 weeks of gestation, or birth weight.

Immunological predictive markers such as ICA, GAD, and IAA can reveal an incipient autoimmune insulin dependent, type 1 diabetes during pregnancy. In our study, only 156 GDM women were analyzed with respect to autoantibodies as this was not included from the start. Our findings that 12 (7.7%) were GAD positive, eight (5.1%) ICA positive and five (3.2%) IA2A positive is close to the findings of Fuchtenbusch (24) who found the respective figures to be 9.5%, 8.5% and 6.2% at delivery, Damm (25) who found 4 of 139 in his Danish population to be ICA-positive, and Metzger (8) who reported an ICA prevalence of 1.6%. Follow-up OGTT was performed in 10 of the 12 women with GAD antibodies. Three of the OGTT values were pathologic. This number is too small for firm conclusions. The value of these autoantibodies to predict future development of type 1 diabetes is reported from several authors. Thus, Fuchtenbusch et al. (24) reported that 2 years postpartum, 29% of those positive for at least one antibody had developed type 1 diabetes. Damm et al. (25) found the predictive value of a positive ICA for a later development of type 1 diabetes to be 75% with a sensitivity of 50% and specificity of 99%. Even if type 1 diabetes after GDM is uncommon, it develops faster than type 2 diabetes and according to Damm et al. makes up as much as 20% of those who develop overt diabetes during the first postpartum period. Thus, it seems reasonable, as proposed by Damm et al. to consider routine screening of women with GDM for GAD and/or ICA, at least in areas with a high incidence of type 1 diabetes.

Eriksson et al. (26) have shown on men and the UKPDS study (27) on men and women that it is possible to delay the development of diabetes and its complications in persons at risk by diet and physical exercise. Thus, it seems reasonable to identify those at risk of developing overt diabetes. Other obvious reasons are the increased risk for the health of the fetus/infant that will diminish when adequate obstetric measurements are taken (28,29). We did not find any of the tested factors in GDM women to be a strong enough predictor for pathologic glucose tolerance at 1 year follow up to permit a selection of women for a specific check program.

We think there is reason enough for a general screening or a direct diagnostic method to identify GDM women.

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