Increasing Incidence of Diabetes After Gestational Diabetes

A long-term follow-up in a Danish population

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OBJECTIVE — To study the incidence of diabetes among women with previous diet-treated gestational diabetes mellitus (GDM) in the light of the general increasing incidence of overweight and diabetes and to identify risk factors for the development of diabetes.

RESEARCH DESIGN AND METHODS — Women with diet-treated GDM during 1978–1985 (old cohort, $n = 241$, also followed up around 1990) or 1987–1996 (new cohort, $n = 512$) were examined in 2000–2002. Women were classified by a 2-h, 75-g oral glucose tolerance test according to the World Health Organization criteria or an intravenous glucagon test supplemented by measurement of GAD antibodies. Historical data from index-pregnancy and anthropometrical measurements were collected.

RESULTS — A total of 481 (63.9%) women were examined (median 9.8 years [interquartile range 6.4–17.2]) after index pregnancy. Diabetes and impaired glucose tolerance (IGT)/impaired fasting glucose were present in 40.0 and 27.0% of women, respectively. In the new cohort, 40.9% had diabetes compared with 18.3% in the old cohort at the 1990 follow-up ($P < 0.0005$). Prepregnancy BMI was significantly higher in the new compared with the old cohort (26.0 [22.5–30.8] vs. 22.9 kg/m^2 [20.2–28.0], $P < 0.0005$). Among others, new-cohort membership, prepregnancy overweight (BMI ≥25 kg/m^2), and IGT postpartum were identified as independent predictors of diabetes by multiple logistic regression analyses.

CONCLUSIONS — The incidence of diabetes among Danish women with previous diet-treated GDM was very high and had more than doubled over a 10-year period. This seems to be due to a substantial increase in BMI in women with GDM.

Diabetes Care 27:1194–1199, 2004

Gestational diabetes mellitus (GDM), defined as abnormal glucose tolerance detected for the first time in pregnancy (1), occurs in 2–3% of all pregnant women in Denmark (2). GDM is a well-known risk factor for developing overt diabetes later in life, especially type 2 diabetes (3–5). Our group has previously found that 34% of Danish women with previous diet-treated GDM had abnormal glucose tolerance 2–11 years after pregnancy (6) compared with 5% in a control group.

Various pregnancy-related factors have been found to predict diabetes, e.g., diagnosis of GDM early in pregnancy, high blood glucose levels at diagnosis, need for insulin treatment during pregnancy, preterm delivery, and an abnormal oral glucose tolerance test (OGTT) 2 months postpartum (6–8). Obesity/overweight is a well-known risk factor for developing diabetes (9), also among women with previous GDM (10). This is notable since obesity is an increasing problem in younger Danish women (11).

Most long-term follow-up studies after GDM are in non-European populations and do not differentiate between women treated with diet or insulin during pregnancy. Since it is well known that insulin-treated GDM women have a very high risk of subsequent diabetes, we decided to exclusively study the prognosis of women treated with diet only to obtain a more homogeneous population.

The aims of the present study were *1*) to determine the long-term incidence of diabetes among Danish women with previous diet-treated GDM, *2*) to describe potential changes in the incidence of diabetes and overweight during the last decades among women with previous GDM, and *3*) to identify risk factors for the development of diabetes.

RESEARCH DESIGN AND METHODS

The old cohort

The "old cohort" comprised 241 women from the center for diabetes and pregnancy, Rigshospitalet, with diet-treated GDM during 1978–1985 who previously participated in a follow-up 2–11 years after index pregnancy (6). All subjects had GDM based on a 3-h, 50-g OGTT during pregnancy (12). The group covered 81% of our diet-treated GDM population from this period, and details have been previously published (6).

The new cohort

The "new cohort" comprised all women ($n = 512$) from the same center with diet-

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Received for publication 30 October 2003 and accepted in revised form 16 February 2004.

Abbreviations: GADA, GAD antibody; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

Table 1—*Baseline characteristics from index pregnancy and routine follow-up for women with previous diet-treated GDM comparing participants and nonparticipants in the 2002 follow-up study*

	Participants	Nonparticipants	*P*
n	481	272	
Age at index pregnancy (years)	31.7 (27.7–35.7)	30.6 (27.8–34.2)	0.114
Prepregnancy BMI (kg/m^2)	25.1 (21.9–29.8)	26.9 (22.0–31.7)	**0.035**
Gestational age at diagnosis (days)	227 (197–249)	227 (197–249)	0.842
Gestational age at birth (days)	274 (267–278)	272 (265–278)	0.171
Fasting plasma glucose at diagnosis (mmol/l)	5.0 (4.5–5.5)	5.1 (4.7–5.7)	0.059
Nordic origin (%)	75.0	76.9	0.552
Follow-up 2 months postpartum (%)	91.9	83.5	**<0.0005**
IGT 2 months postpartum (%)	21.2	23.6	0.478
Diabetes 2 months postpartum (%)	2.7	4.8	0.152
Attendance to routine follow-up OGTT (%)†	87.5	65.8	**<0.0005**
Diabetes at latest routine follow-up (%)	24.4	36.8	**0.001**

Data are median (interquartile range) unless otherwise indicated. †Women with previous GDM and without known diabetes are offered regular OGTT after delivery with 1- to 2-year intervals. Boldface data are significant.

treated GDM between 1987 and 1996. GDM diagnosis was based on a 3-h, 75-g OGTT (13).

During 1986 the 50-g OGTT was replaced by a 75-g test, and women from 1986 were not included in the present follow-up study. Both OGTTs were defined as abnormal if two or more of seven values during the test exceeded 3 SDs above the mean for a group of normal-weight nonpregnant women without family history of diabetes examined in exactly the same manner (13) (e.g., fasting venous plasma glucose 6.4 and 6.2 and 2-h plasma glucose 7.6 and 8.9 mmol/l, respectively) (12). GDM screening was based on risk factors (family history of diabetes, prepregnancy overweight [>20% overweight] [14] or BMI ≥27 kg/m^2 [from 1994], previous macrosomic infant [birth weight ≥4,500 g], glucosuria, previous GDM, and age ≥35 years [from 1994]) and fasting blood glucose (capillary whole blood ≥4.1 or capillary plasma ≥4.7 mmol/l) (13,15).

Women with GDM were routinely offered an OGTT 2 months postpartum and, subsequently, in 1- to 2-year intervals, unless diabetes was diagnosed.

Follow-up

The women were invited by mail to take part in our follow-up study. Nonresponders were contacted again by phone or mail. Sixty-four percent (*n* = 481; 151/241 of old cohort, 330/512 of new cohort) of the total population was included. Reasons for not participating were refusal (*n* = 167), no response (*n* = 71), death (*n* = 8), severe illness other than diabetes (*n* = 7), pregnancy (*n* = 6), and emigration (*n* = 13). Characteristics for participants and nonparticipants are presented in Table 1.

OGTT

The women attended the center between 0800 and 1000 after a 10 h fasting, including no smoking or drinking. Two blood samples were drawn from an antecubital vein for measurement of plasma glucose and serum GAD antibodies (GADAs). Women without known diabetes also had a 2-h, 75-g OGTT with measurement of 2-h venous plasma glucose. Five percent of the tests were based on capillary whole blood glucose due to technical problems obtaining venous samples.

Glucagon test

Women reporting insulin-treated diabetes (*n* = 22) were examined by a 6-min glucagon test, where 1 mg glucagon (Glucagen; Novo Nordisk) was injected intravenously to evaluate pancreatic β-cell function (16). If fasting serum C-peptide was <300 pmol/l and 6-min C-peptide was <600 pmol/l, then the woman was classified as having type 1 diabetes.

Biochemical methods

Plasma glucose was measured by the glucose oxidase method using an automated colorimetric method on a Cobas Mira analyzer. Serum C-peptide was measured by a fluoroimmunometric assay using monoclonal antibodies on an AutoDelfia from Wallac/Perkin-Elmer (Allerød, Denmark).

GADAs were detected by a radioimmunoassay (Diamyd Anti-GAD-65 RIA; Diamyd Diagnostics, Stockholm, Sweden) according to the protocol provided by the manufacturer. Sera were run in duplicate, and the results were read on a γ counter (Wizard 1470; Wallac/PerkinElmer) and calculated from a standard curve. The cutoff limit was 9.5 units/ml, and the intra- and interassay coefficients of variation were 0.024 and 0.036, respectively.

Anthropometrical measurements

The women were classified as normal weight (BMI <25 kg/m^2), overweight (BMI 25–30), or obese (BMI ≥30).

Historical data

Historical data were collected from local medical records. The glucose values from the diagnostic OGTT in pregnancy have been primarily measured in capillary blood and plasma but also as venous plasma for a shorter period. To compare the capillary blood glucose with plasma glucose, the capillary plasma glucose values were divided by a factor of 1.14 (17), whereas the venous plasma values were used uncorrected, as in our previous study (6). In the old cohort, the postpartum 50-g OGTT was evaluated as in pregnancy (6). The postpartum OGTT in the new cohort and the OGTTs from the 1990 follow-up for the old cohort and from the present follow-up for both cohorts were all 75-g OGTTs and evaluated according

Table 2—*Follow-up characteristics for the old cohort in 1990 and 2002 and for the new cohort in 2002*

	Old cohort 1990	New cohort 2002	Old cohort 2002
n	241	330	151
Age (years)	35.9 (31.8–40.2)	39.8 (35.8–44.4)*	48.8 (44.6–53.7)†
Follow-up (years)	6.0 (4.6–7.7)	7.4 (5.6–9.9)*	18.8 (17.5–20.6)†
BMI (kg/m^2)	25.1 (21.5–30.1)	28.5 (24.2–33.1)*	27.0 (23.4–31.8)
Normal glucose tolerance	150 (62.2)	108 (32.7)*	51 (33.8)
IGT/IFG	47 (19.5)	87 (26.4)	43 (28.5)
Diabetes	44 (18.3)	135 (40.9)*	57 (37.7)
Diabetic OGTT	20 (8.3)	65 (19.7)	21 (13.9)
Known type 2 diabetes	15 (6.2)	57 (17.3)	28 (18.5)
Known type 1 diabetes	9 (3.7)	13 (3.9)	8 (5.3)

Data are median (interquartile range) or *n* (%). *$P < 0.0005$, old cohort 1990 vs. new cohort 2002; †$P < 0.0005$, old cohort 2002 vs. new cohort 2002. Diabetes: fasting plasma glucose ≥7.0 mmol/l or 2-h plasma glucose ≥11.1 mmol/l; IGT: fasting plasma glucose <7.0 mmol/l and 2-h plasma glucose ≥7.8 and <11.1 mmol/l; IFG: fasting plasma glucose ≥6.1 and <7.0 mmol/l and 2-h plasma glucose <7.8 mmol/l (16).

to the 1999 World Health Organization criteria (18).

The study was approved by the Copenhagen ethical committee [J.nr. (KF) 11-082/01] and conducted according to the Helsinki Declaration. All participants gave signed content before examination.

Statistical analysis

Data are given as median and interquartile range or number (percent). The χ^2 test was used for comparison of frequencies, while medians between groups were compared by the Mann-Whitney *U* test. Uni- and multivariate logistic regression were applied to examine the relationship between dependent (development of diabetes) and the following independent variables, using manual backward elimination and forward selection: new/old cohort, Nordic origin, prepregnancy BMI, smoking, parity, family history of diabetes, GDM diagnosis before 24 gestational weeks, quartiles of fasting glucose from the diagnostic OGTT in pregnancy, preterm delivery (gestational age <37 weeks), age at delivery, impaired glucose tolerance (IGT) postpartum (old cohort: two or more values above mean + 3 SD; new cohort: 2-h glucose ≥ 7.8 mmol/l), and age at follow-up. Women with overt diabetes postpartum (within 6 months after pregnancy) were excluded from the logistic regression analyses ($n = 12$). The association between the independent variables and the development of diabetes is presented as crude and adjusted odds ratios (ORs) and 95% CI. In one model, the dependent variable was diabetes at follow-up for the old cohort in 1990 and for the new cohort in 2002, 3.5–15 years after index pregnancy. In three other models, the dependent variable was diabetes at follow-up in 2002 (type 1 or type 2 diabetes, type 2 diabetes, or type 1 diabetes), 3.5–23.2 years after index pregnancy. The analyses were adjusted for length of follow-up. Life table analysis was not applied due to individual variation in the regularity and intervals of OGTTs after pregnancy.

A two-sided *P* value <0.05 was considered significant. SPSS for Windows, version 11.0, was used for statistical analysis.

RESULTS — The total cohort of 481 women was followed for 9.8 years (interquartile range 6.4–17.2), and the median age at follow-up was 42.9 years (37.7–47.8). Diabetes was present in 192 (39.9% [95% CI 35.5–44.3]) and IGT/impaired fasting glucose (IFG) in 130 (27.0% [23.1–31.0]) women. Twenty-one had type 1 and 171 type 2 diabetes. One woman with a fasting C-peptide of 306 pmol/l and a 6-min C-peptide of 421 pmol/l had high GADAs and was classified as having type 1 diabetes. GADAs were detected in 22 of 453 women (14 type 1 diabetic, 3 type 2 diabetic, 2 with IGT/IFG, and 3 normal glucose tolerant). Twelve of the 442 women (2.7%) examined postpartum had overt diabetes; all 12 had diabetes at follow-up. The median BMI was 27.9 kg/m^2 (24.1–32.9). BMI >25 kg/m^2 was found in 60.9%, and 31.6% were obese.

Characteristics of the old and the new cohort at index pregnancy

The new cohort was older (33.0 years [28.6–36.4] vs. 30.0 [26.1–33.6], $P < 0.0005$) and had a higher prepregnancy BMI (26.0 kg/m^2 [22.5–30.8] vs. 22.9 [20.2–28.0], $P < 0.0005$). Two screening criteria were more frequent in the new cohort: family history of diabetes (47.8 vs. 31.5%, $P < 0.0005$) and overweight (50.2 vs. 25.3%, $P < 0.0005$). In the new cohort, there were fewer Nordic Caucasians (71.5 vs. 88.7%, $P < 0.0005$) and GDM was diagnosed earlier in pregnancy (224 days [range 195–245] vs. 237 [209–258], $P < 0.0005$). There were no significant differences regarding the screening criteria glucosuria (43.2% in new cohort vs. 44.8% in old cohort), macrosomia (8.8 vs. 6.2%), or previous GDM (4.4 vs. 7.1%).

Characteristics of the old and new cohorts at follow-up

The incidence of diabetes was more than twofold higher in the new cohort compared with the old cohort at the 1990 follow-up ($P < 0.0005$), whereas similar rates of diabetes were found in comparison with the old cohort at the 2002 follow-up (Table 2).

BMI was significantly higher in the new cohort compared with the old cohort in 1990, while no significant difference was present in 2002. Women in the new cohort were older at the 2002 follow-up than women in the old cohort at the 1990 follow-up, and they were followed for 1 year longer. Median age and duration of follow-up were both ~10 years more for the old cohort in 2002 compared with the new cohort.

Among women from the old cohort included in the present follow-up study, 15% had diabetes at follow-up in 1990 and another 23% subsequently developed diabetes. Seventeen of 27 (63%) with IFG and/or IGT at follow-up in 1990 had developed diabetes at the latest follow-up.

Multiple logistic regression

Table 3 presents crude and adjusted ORs for the association between various independent variables and development of diabetes at follow-up in 1990 for the old cohort and 2002 for the new cohort. The variables independently associated with diabetes were: new cohort membership, prepregnancy overweight/obesity, early diagnosis of

Table 3—*Crude and adjusted ORs for independent variables tested in multiple logistic regression with the dependent variable overt diabetes at follow-up in 1990 for the old cohort and in 2002 for the new cohort*

	Crude OR (95% CI)	Adjusted OR (95% CI)*
n (diabetes/total†)	164/556	142/506
New cohort 2002 vs. old cohort 1990	3.1 (2.1–4.7)‡	3.1 (1.9–5.3)‡
Prepregnancy BMI <25 kg/m^2	1.0	1.0
Prepregnancy BMI ≥25 and <30 kg/m^2	2.4 (1.5–3.8)‡	2.0 (1.1–3.4)§
Prepregnancy BMI ≥30 kg/m^2	3.2 (2.0–5.0)‡	2.6 (1.5–4.5)§
GDM diagnosis before gestational age of 24 weeks	3.7 (2.1–6.3)‡	2.3 (1.2–4.5)‖
Fasting plasma glucose at diagnosis of GDM (mmol/l)¶	2.1 (1.3–3.2)§	2.5 (1.5–4.2)‡
IGT 2 months postpartum†	3.9 (2.5–6.0)‡	5.8 (3.3–9.9)‡
Preterm delivery (gestational age <37 weeks)	2.2 (1.3–3.8)§	—
Age at follow-up	1.1 (1.0–1.1)‡	—
Family history of diabetes	1.5 (1.0–2.1)‖	—
Other ethnic origin than Nordic	1.7 (1.1–2.6)‖	—

Only statistically significant ORs are presented. *Adjusted for the other independent variables in the final model and follow-up length as a noncontinuous variable. †The total number includes women from the old cohort at the 1990 follow-up and from the new cohort at the 2002 follow-up. Women with overt diabetes postpartum were not included in the analyses ($n = 12$). As a result of the OGTT, postpartum is included in the final model, and as only 87.5% had an OGTT postpartum, the total number of women included in the final model was lower than the total number of all the participants. The final model only includes women with available data on all the variables. ‡$P < 0.0005$; §$P < 0.01$; ‖$P < 0.05$. ¶Highest quartile of fasting glucose compared with the three lowest quartiles: 75th percentile = 5.6 mmol/l.

GDM, high fasting glucose at the diagnostic OGTT, and IGT postpartum.

Table 4 presents three models, where the dependent variable is either diabetes (both type 1 and 2), type 2 diabetes, or type 1 diabetes at latest follow-up in 2002.

IGT postpartum, early diagnosis of GDM, prepregnancy overweight/obesity, and fasting glucose at diagnosis were predictors for diabetes in general and for type 2 diabetes in particular. Type 2 diabetes was also predicted by the screening criteria family history of diabetes. Fasting glucose at the postpartum examination was not related to follow-up diabetes status. An ethnic origin different from Nordic did not predict diabetes when adjusting for prepregnancy BMI. The only significant predictors for later type 1 diabetes were preterm delivery and IGT postpartum.

CONCLUSIONS — Forty percent of a Danish population of women with previous diet-treated GDM had developed diabetes at a median of 10 years after pregnancy. This incidence is more than ten times higher than in the 30- to 60-year-old female background population (19). The risk of developing diabetes after GDM has more than doubled during the last decade. Thus, in contrast to previous studies from Scandinavia (6,20), where relatively low incidences of diabetes were found in women with previous GDM, the incidence is now comparable to studies from other parts of the world (5). The most obvious reason is the increase in BMI before and after index pregnancy found in the present study, probably reflecting a global epidemic (21). Accordingly, it has recently been found that the increased incidence of IGT and diabetes in a Danish cohort of 60-year-old women and men could be fully explained by the increasing BMI (22). It is therefore not surprising that we now find overweight and obesity to be significant risk factors for later development of diabetes, which is in agreement with previous studies (5). Indeed, 61% of our women were overweight, with more than half fulfilling the criteria for obesity. This proportion is three times as high as in the background population of Danish women aged 30–60 years (11).

Obviously some changes in clinical practice happen over a period of 20 years, such as the change from the 50- to 75-g OGTT as the diagnostic test for GDM. When this change took place, it was aimed to define the GDM criteria in the same way as the background population.

Table 4—*Adjusted ORs for the independent variables tested in multiple logistic regression with diabetes, known type 2 diabetes, or known type 1 diabetes as the dependent variable at follow-up in 2002*

	Diabetes	Type 2 diabetes	Type 1 diabetes
	Adjusted OR (95% CI)*	Adjusted OR (95% CI)*	Adjusted OR (95% CI)*
n in full model (diabetes/total)†	162/425	143/417	16/430
Prepregnancy BMI <25 kg/m^2	1.00	1.00	—
Prepregnancy BMI ≥25 and <30 kg/m^2	2.2(1.3–3.8)‡	2.6(1.5–4.7)‡	—
Prepregnancy BMI ≥30 kg/m^2	3.0(1.7–5.2)§	4.2(2.3–7.4)§	—
Family history of diabetes	—	1.9(1.2–3.2)‡	—
Diagnosis before gestational age 24 weeks	3.6(1.7–7.3)‡	2.9(1.5–5.9)‡	—
Fasting plasma glucose at diagnosis of GDM (mmol/l)¶	2.3(1.3–3.8)‡	2.1(1.2–3.6)‡	—
IGT postpartum	4.4(2.5–7.7)§	3.5(2.06.0)§	2.8(1.0–7.9)‖
Preterm delivery	—	—	3.2(1.1–9.9)‖

Only statistically significant ORs are presented. *Adjusted for the other independent variables in the final model, including cohort effect (old versus new cohort) and follow-up length as a continuous variable. †Women with overt diabetes postpartum were not included in the analyses ($n = 12$). The total number is the number of women from both cohorts in 2002 included in the final model and with available data on all the variables. As a result of the OGTT, postpartum is included in the final models, and as only 87.5% had an OGTT postpartum, the total number of women included in the final models was lower than the total number of all the participants. ‡$P < 0.01$; §$P < 0.0005$; ‖$P < 0.05$. ¶Highest quartile of fasting glucose compared with the three lowest quartiles: 75th percentile = 5.6 mmol/l.

Nevertheless, comparison of the cohorts might be biased by the different diagnostic tests. Our prevalence of GDM has remained rather stable over the years, with an increasing tendency during the 1990s, indicating no selection toward a more severe metabolic disturbance in the new cohort. The new cohort was older and more overweight before pregnancy, which is in accordance with the trend seen in the Danish background population (11). Also, more women had a family history of diabetes, which did not turn out to be an independent predictive factor for the development of overt diabetes in general, although it did predict the development of type 2 diabetes. However, when adjusting for prepregnancy BMI, family history of diabetes, and other pregnancy-related risk factors, we still found a significant difference in overt diabetes between the old and new cohort. Thus, it is not likely that the very significant predictive factor "cohort effect" (OR 3.1) solely could be explained by the differences in the screening and diagnostic tests for GDM used over time. In contrast, the cohort effect might reflect a change to a more sedentary lifestyle. Lifestyle has recently been found to influence the risk of developing diabetes and obesity, and a more physically active lifestyle can reduce this risk (23). An active lifestyle in combination with a low-calorie diet can also reduce the high risk for IGT/IFG to progress to overt diabetes by >50% (24). IGT/IFG was diagnosed in 19.5% of the old cohort at follow-up in 1990 and 26.4% in the new cohort. More than 60% of women with IGT/IFG in 1990 developed diabetes in the following years, indicating that the number of women who develop diabetes will progressively increase. Despite an offer of regular OGTTs after pregnancy, half of the cases of diabetes were undiagnosed until the present study. These women therefore comprise a group with a markedly increased morbidity (25).

Few studies have looked at different types of diabetes after GDM. In agreement with our previous study (6), we found that type 1 and type 2 diabetes were common. This probably reflects that type 1 diabetes is relatively frequent in our primarily Nordic Caucasian population in comparison with, for example, Hispanic Americans. This study is to our knowledge the first to study risk factors for either type 2 or type 1 diabetes. The best predictor for diabetes in general was IGT postpartum, in accordance with previous studies (6,26). Preterm delivery was an independent risk factor for the development of type 1 but not type 2 diabetes. This finding is of interest, since it has been shown for pregnant women with both type 1 diabetes and GDM that increasing glucose levels increase the risk of spontaneous preterm delivery (27,28).

The women who did not participate in the study were markedly heavier and more often had diabetes at routine follow-up than participating women. Thus, we suggest that the demonstrated incidence of diabetes is a conservative estimate compared with what would be expected if the whole population of women with previous GDM had been examined.

Women with insulin-treated GDM comprised 16.1 and 15.1% of women with GDM during 1978–1985 and 1987–1996, respectively ($P = 0.69$), and were not included because they are likely to have a more severe form of GDM, resulting in even higher estimates of subsequent overt diabetes.

In conclusion, we found a doubling in the incidence of diabetes and IGT/IFG over a 10-year period. Our study supports previous findings that women with GDM are at high risk for subsequent diabetes. The risk is further increased if obesity is present before pregnancy. Furthermore, we found an increasing incidence of overweight among women with GDM. Women with previous GDM represent a target group for intervention to postpone or prevent the development of overt diabetes.

Acknowledgments— This research was supported by the Danish Medical Research Counsil, Copenhagen University, the Danish Diabetes Association, Handelsgartner Ove Villiam Buhl Olesen og ægtefælle Edith Buhl Olesens Mindelegat, and Dagmar Marshalls Fond.

The authors thank the laboratory staffs at the Department of Obstetrics (Rigshospitalet) and Steno Diabetes Center for skillful technical assistance and statistician Svend Kreiner (Biostatistical Institute, Copenhagen University) for statistical assistance.

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