

Determinants of Mild Gestational Hyperglycemia and Gestational Diabetes Mellitus in a Large Dutch Multiethnic Cohort

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OBJECTIVE — The purpose of this study was to identify independent determinants of mild gestational hyperglycemia (MGH) and gestational diabetes mellitus (GDM) and to assess the correlation between fasting glucose and C-peptide levels among control, MGH, and GDM women.

RESEARCH DESIGN AND METHODS — A total of 1,022 consecutive women were evaluated with a 1-h 50-g glucose challenge test (GCT) at between 16 and 33 weeks of gestation. Women with a capillary whole-blood glucose ≥ 7.8 mmol/l in the GCT underwent a 3-h 100-g oral glucose tolerance test (OGTT). On the basis of a positive GCT, the women with a positive OGTT were classified as GDM, whereas the women with a negative OGTT were classified as MGH. The following data were collected for all women: age, prepregnancy BMI, ethnicity, clinical and obstetric history, pregnancy outcome, and C-peptide level.

RESULTS — A total of 813 women (79.6%) were normal, 138 (13.5%) had MGH, and 71 (6.9%) had GDM. There was a stepwise significant increase in mean fasting glucose (3.6 ± 0.4 , 3.9 ± 0.4 , and 4.7 ± 0.7 mmol/l, respectively) and C-peptide level (0.60 [0.1–2.4], 0.86 [0.3–2.0], and 1.00 [0.5–1.6] nmol/l, respectively) among the three diagnostic groups. Maternal age, non-Caucasian ethnicity, and prepregnancy BMI were associated with GDM, whereas only maternal age and prepregnancy BMI were associated with MGH. A positive correlation between levels of fasting glucose and C-peptide was found in control women ($r = 0.39$ [95% CI 0.31–0.46]). A similar result was seen in MGH women ($r = 0.38$ [95% CI 0.23–0.52]), whereas the correlation between fasting glucose and C-peptide was nearly lost in GDM women ($r = 0.14$ [CI –0.09 to 0.36]). The fasting C-peptide-to-glucose ratio was reduced by 60% in GDM patients versus control subjects and MGH patients (0.41 ± 0.25 vs. 0.70 ± 0.20 and 0.73 ± 0.23 , $P < 0.001$).

CONCLUSIONS — Of the well-known independent determinants of GDM, only maternal age and prepregnancy BMI were associated with MGH. It appears that additional factors promoting loss of β -cell function distinguish MGH from GDM. One of these factors appears to be ethnicity.

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The extra energy requirement of one pregnancy amounts to $\sim 80,500$ kcal (1). Throughout pregnancy, glucose is the primary metabolic substrate for the growing fetus, both for its energy needs as well as for carbon accretion (2). Gestational diabetes mellitus (GDM) occurs as a result of metabolic maladaptation to insulin resistance caused by the hormonal changes of pregnancy (3,4). Therefore, GDM represents a susceptibility model to study glucose abnormalities in the setting of insulin resistance, without interference from side effects of long-term hyperglycemia.

To describe in more detail gestational glucose abnormalities, we studied women with a positive 50-g oral glucose challenge test (GCT) followed by a positive 3-h 100-g oral glucose tolerance test (OGTT) and women with a positive GCT followed by a negative OGTT. We classified the latter group as mild gestational hyperglycemia (MGH).

The aim of the present study was to characterize gestational hyperglycemia by identifying, in a large Dutch hospital (out-patient) population, the women suffering from MGH and GDM. We identified independent determinants of MGH and GDM and studied the correlation between glucose and C-peptide in MGH, GDM, and control subjects.

RESEARCH DESIGN AND METHODS

Consecutive pregnant women (1,059, over a study period of 30 months [1998–2001]) were recruited from the outpatient clinic of obstetrics and gynecology of our hospital. The patients were referred due to a history of delivery by caesarean section (30.6%), high-risk pregnancy (10.5%), stillborn fetus (4.4%), or multiple pregnancy (6.5%), or they were referred for (preexistent) hypertension (6.4%), maternal age (5.6%), treatment of infertility (3.6%), suspicion of GDM (3.5%), or other obstetrical pathology (28.9%). Diabetic pa-

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Abbreviations: GCT, glucose challenge test; GDM, gestational diabetes mellitus; MGH, mild gestational hyperglycemia; OGTT, oral glucose tolerance test.

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

Table 1—General characteristics of control, MGH, and GDM women

	Control subjects	MGH women	GDM women	P
n	490	138	71	
Maternal age (years)	33.2 ± 5.1	35.2 ± 5.3*	35.2 ± 5.0†	<0.001
Gestational age at diagnosis of GDM (weeks)	25.6 ± 3.2	25.8 ± 3.3	25.2 ± 4.5	0.489
Prepregnancy BMI (kg/m ²)	24.2 ± 4.7	25.6 ± 6.0†	28.3 ± 4.7*‡	<0.001
Ethnicity (Caucasian/non-Caucasian)	253/237 (52/48)	67/71 (49/51)	18/53 (25/75)*§	<0.001
Family history of diabetes	113 (223)	29 (22)	23 (33)	0.178
Parity	1.1 (0–8)	1.4 (0–11)	1.8 (0–6)*	0.001
Pregnancy-induced hypertension	18 (4)	9 (6)	8 (11)§	0.015
Prepregnancy hypertension	11 (2)	4 (3)	2 (3)	0.886
Obstetric history				
Spontaneous abortion	129 (26)	37 (27)	23 (32)	0.530
Fetal loss	53 (11)	19 (14)	10 (14)	0.515
Infant birth weight (percentile)	55 ± 7	53 ± 7	79 ± 11*†	<0.001
Apgar score ≤6 at 5 min	7 (1.6)	2 (2.0)	4 (6.3)¶	0.078
C-peptide (t = 0 min; GCT) (nmol/l)	0.60 (0.1–2.4)	0.86 (0.3–2.0)*	1.00 (0.5–1.6)*‡	<0.001
Glucose (t = 0 min; GCT) (mmol/l)	3.6 ± 0.4	3.9 ± 0.4*	4.7 ± 0.7*#	<0.001
Glucose (t = 60 min; GCT) (mmol/l)	61 ± 1.0	8.5 ± 0.6*	9.8 ± 1.2*#	<0.001

Data are means ± SD, n (%) or median (range). *P < 0.001 vs. control subjects; †P < 0.01 vs. control subjects; ‡P < 0.005 vs. MGH women; §P < 0.005 vs. control subjects; ¶P < 0.05 vs. MGH women; #P < 0.001 vs. MGH women.

tients (n = 11) were excluded from the protocol. Informed consent was obtained, and the study was approved by the hospital's ethics committee.

Obstetric history, family history of diabetes, and weight before pregnancy were obtained from all patients. As indicators of pregnancy outcome, we studied birth weight, expressed as a percentile specific for sex and duration of gestation (5), and Apgar scores at 1 and 5 min after birth.

Glucose tolerance tests and diagnostic criteria

All women had a 50-g GCT at 16–33 weeks of gestation, performed in the morning after a 12-h overnight fast (6). Fasting glucose was measured in venous whole blood, with a capillary whole blood glucose measurement 1 h later. If the latter yielded a value of ≥7.8 mmol/l, a 3-h 100-g OGTT followed within the next 2 weeks. Fasting glucose was measured in venous whole blood, followed by a capillary whole-blood glucose measurement 1, 2, and 3 h after 100 g glucose. GDM was diagnosed when two or more glucose values equaled or exceeded 4.6, 9.6, 8.2, and 7.3 mmol/l, respectively. We converted the 1997 American Diabetes Association criteria (7) according to the data published by Alberti and Skrabalo (8).

Analytical methods

A standard radioimmunoassay kit method was used to measure fasting se-

rum C-peptide (Immulite C-Peptide; EURO/DPC, Llanberis, U.K.; overall coefficients of variation were 14 and 8% at 0.7 and 1.7 nmol/l, respectively) (9). Whole-blood glucose was determined by a hexokinase method using a glucose analyser (EBIO model 6666; Eppendorf, Hamburg, Germany).

Definitions

Ethnicity was assigned on the basis of three criteria: country of birth of the individual, the mother, and the father. It was coded according to the definitions used by the O+S, the Amsterdam bureau of social research and statistics (10). Ethnicity was categorized as Caucasian (512 [48.4%]), sub-Saharan African (174 [16.5%]), Northern African (120 [11.3%]), Armenian (58 [5.4%]), Asian (55 [5.2%]), and others (140 [13.2%]).

BMI (kg/m²) before pregnancy was calculated by using the most recent self-reported weight before conception. Obesity was defined as a BMI ≥27 kg/m² (11). Pregnancy-induced hypertension was defined as an increase in diastolic blood pressure to >90 mmHg (measured using a Korotkoff 5; Speidel & Keller, Jungingen, Germany) in the second half of pregnancy (12). Macrosomia was defined as a birth weight exceeding the 90th percentile (13). We defined a neonate to be at risk when the Apgar score at 5 min was ≤6 (14). We introduced the term MGH to

describe women who had a positive GCT followed by a negative OGTT.

Statistical methods

In our analysis, the following variables were included: maternal and gestational age, prepregnancy BMI and obesity, ethnicity (Caucasian versus non-Caucasian), family history of diabetes, parity, history of spontaneous abortion and of fetal loss, pregnancy/induced hypertension, birth weight (percentiles), Apgar score, C-peptide, and glucose. Variables with nonnormal distribution (e.g., C-peptide) were log-transformed before statistical analysis. To compare variables among control, MGH, and GDM women, data were analyzed using one-way analysis of variance and the Kruskal-Wallis test where appropriate. The Bonferroni *t* method or the Mann-Whitney *U* test were used as post hoc tests. To compare variables such as C-peptide and glucose among the three diagnostic groups, which were matched by prepregnancy BMI, we used analysis of covariance, with prepregnancy BMI as covariate.

We used a multiple logistic regression model to identify independent determinants of MGH and GDM. The value for entry in the logistic regression model was *P* = 0.10. The following variables were considered as possible determinants: maternal age, ethnicity, parity, pregnancy-induced hypertension, and prepregnancy BMI.

Table 2—Results of logistic regression analysis: determinants of MGH and GDH

	MGH women (n = 138)		GDM women (n = 71)	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Maternal age (1 year)	1.09 (1.04–1.13)	<0.001	1.09 (1.03–1.15)	0.002
Ethnicity (non-Caucasian)	1.14 (0.74–1.75)	0.560	2.47 (1.33–4.60)	0.004
Parity (per 1 subject)	1.03 (0.89–1.19)	0.674	0.99 (0.81–1.21)	0.938
Pregnancy-induced hypertension (yes)	1.60 (0.68–3.76)	0.280	2.15 (0.79–5.83)	0.134
Prepregnancy BMI (1 kg/m ²)	1.05 (1.01–1.09)	0.014	1.13 (1.07–1.19)	<0.001

Two-sided P values are reported, with P = 0.05 taken as the level of statistical significance. All statistical procedures were performed using SPSS version 9.0 for Windows (SPSS, Chicago, IL).

We used bivariate analysis to determine reference ranges of combined fasting glucose and C-peptide levels, i.e., the 95% isodensity ellipse of the distribution, and to calculate the absolute correlation coefficient between the mentioned variables (15). The calculation was according to Tatsuoka (16), using the software package EVAL-kit (CKCHL Twee Steden Ziekenhuis, Tilburg, the Netherlands).

RESULTS— A total of 1,059 eligible women gave informed consent to participate in the study. Four patients suffered from Graves disease. Twenty-two patients were unable or unwilling to follow the protocol, i.e., glucose concentration measured too late, one or several glucose measurements missed, or refusal to finish the tolerance test. Eleven women with newly detected type 2 diabetes could not enter the study, leaving 1,022 patients.

GDM was diagnosed in 71 women (6.9%) and MGH in 138 women (13.5%). From the remaining 813 women with a negative GCT, 490 were randomly selected to serve as control subjects. Therefore, the final study population consisted of 699 women (66%) who entered the study between 16 and 33 weeks of gestation.

Clinical and laboratory characteristics of control, MGH, and GDM subjects are outlined in Table 1. The five mentioned non-Caucasian subgroups were too small to permit any valid mutual comparisons. Therefore, these women were combined as non-Caucasians. The relatively large proportion of non-Caucasians in the study group reflects the population constitution in the area (17). Table 1 also shows the results of multiple-comparison procedures examining possible determi-

nants of MGH and GDM. GDM women, compared with control subjects, had markedly higher (P < 0.05) maternal age, prepregnancy BMI, rate of non-Caucasian origin, parity, and pregnancy-induced hypertension, whereas only maternal age and prepregnancy BMI were increased (P < 0.05) in MGH versus control women. The prevalence of family history of diabetes was highest but not significantly different in GDM women compared with control and MGH women. In contrast to MGH women, GDM women were at significantly increased risk for delivery of a macrosomic infant (13/138 [9.4%] vs. 25/71 [35.2%]) and/or an infant with a low Apgar score at 5 min.

Determinants that were (close to) significant (P < 0.10) in the univariate analysis were entered into a multiple logistic regression analysis. Table 2 shows the results of multivariate analyses with MGH and GDM as the dependent variable. Maternal age, ethnicity, and prepregnancy BMI were significantly associated with GDM and explained 19% of its variance. Maternal age and prepregnancy BMI were significantly associated with MGH and explained 7% of its variance.

Fasting glucose, glucose at 60 min during GCT, and fasting C-peptide were significantly increased (P < 0.001) in MGH women by 8, 39, and 43%, respectively, compared with control subjects

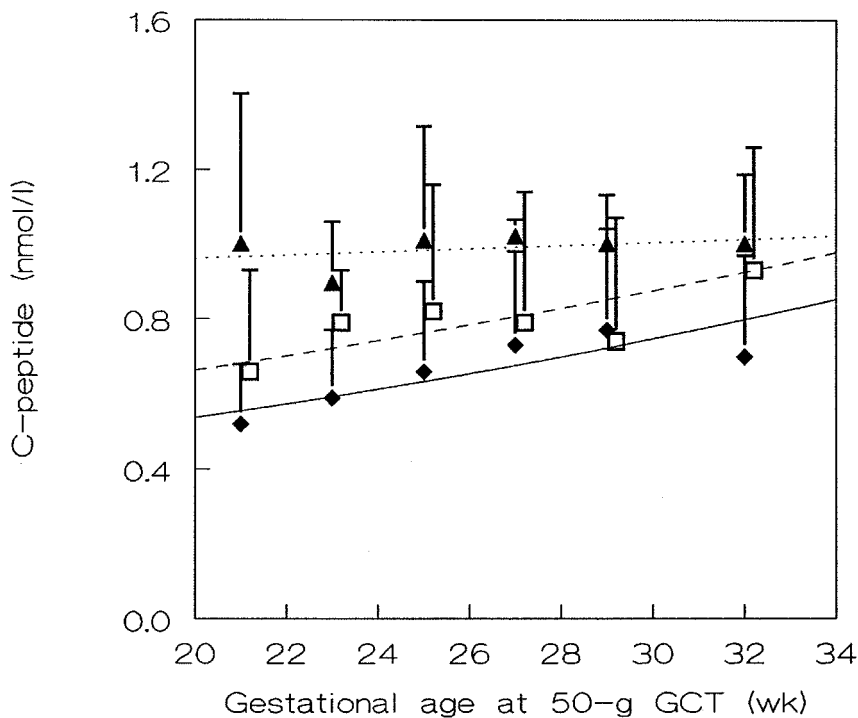


Figure 1—Course of fasting C-peptide level in relation to gestational age of control (◆), MGH (□), and GDM (▲) women. Each symbol represents the mean (±SD) C-peptide of women who entered the study during the indicated interval of 2 weeks.

Table 3—Simultaneous interpretation of fasting glucose and C-peptide

	Control subjects	MGH women	GDM women
n	487	136	71
r (95% CI)	0.39 (0.31–0.46)	0.38 (0.23–0.52)	0.14 (–0.09 to 0.36)
Standard principal component			
Slope ($\times 10^{-6}$)	0.70	0.73	0.41
y-Intercept (nmol/l)	–1.86	–2.00	–0.87
SE of estimated (Syx)	0.20	0.23	0.25

(Table 1). In parallel, fasting glucose, glucose at 60 min during GCT, and fasting C-peptide were significantly increased ($P < 0.001$) in GDM women by 31, 61, and 67%, respectively, compared with control subjects. Similar results were obtained when the difference in prepregnancy BMI was adjusted for (data not shown). Figure 1 displays the course of fasting C-peptide level during gestational age among the three diagnostic groups. It seems that fasting C-peptide level of control subjects becomes markedly increased during gestation and that for all pregnant women who were at 20–33 weeks of gestation, MGH induced a significant (21%) upward displacement of the C-peptide curve as compared with control subjects. The highest level of fasting C-peptide (~ 1 nmol/l) with the lowest degree of increase during pregnancy was seen in GDM women.

The results of bivariate statistical analyses for the combination of fasting glucose and C-peptide are displayed in Table 3. Women with significantly outlying glucose or C-peptide values were ex-

cluded, resulting in omission of these data for three control and two MGH women. The data provided evidence of a positive correlation between fasting glucose and C-peptide for the control subjects ($r = 0.39$ [95% CI 0.31–0.46]), resulting in a slim reference ellipse (Fig. 2A). A similar result was seen for MGH women ($r = 0.38$ [0.23–0.52]) (Fig. 2B). The correlation was nearly lost in GDM women (0.14 [–0.09 to 0.36]), with the result that the shape of the reference ellipse approached a circle (Fig. 2C). In addition, the fasting C-peptide-to-glucose ratio, i.e., the slope of the major axis of the ellipse (the standard principal component), was significantly reduced ($P < 0.001$) in GDM women compared with control subjects (0.41 ± 0.25 and 0.70 ± 0.20 , respectively), whereas the ratio was similar ($P = 0.17$) in both MGH and control women (0.73 ± 0.23 and 0.70 ± 0.20 , respectively). After including the five outliers, similar results were seen for the bivariate statistical analyses (data not shown).

CONCLUSIONS— This study was undertaken to characterize determinants of MGH and GDM and to assess the extent of correlation between glucose and C-peptide in control, MGH, and GDM women.

Considering the high fertility rate in all immigrant groups, the ethnic composition (Caucasian/non-Caucasian) in both the control and MGH women (52/48% and 49/51%, respectively) was quite similar to the female population of the four town boroughs in close proximity to the hospital (57/43%). The observed increase of the C-peptide level during pregnancy is well documented (18). To the best of our knowledge, there are no other published data specifically addressing the association between fasting glucose and C-peptide from a cohort of pregnant women.

Overall C-peptide and glucose concentrations were significantly elevated in MGH compared with control women. However, both levels were lower than those of the GDM women. Furthermore, our results suggested that C-peptide levels in MGH women, in contrast to GDM women, paralleled those in control subjects during pregnancy. Both the correlation coefficient between fasting glucose and C-peptide and the fasting C-peptide-to-glucose ratio were found to be similar in MGH and control women. These findings suggest a near-normal pattern of glucose-triggered insulin release in MGH. The present study identified two determinants of MGH: maternal age and BMI.

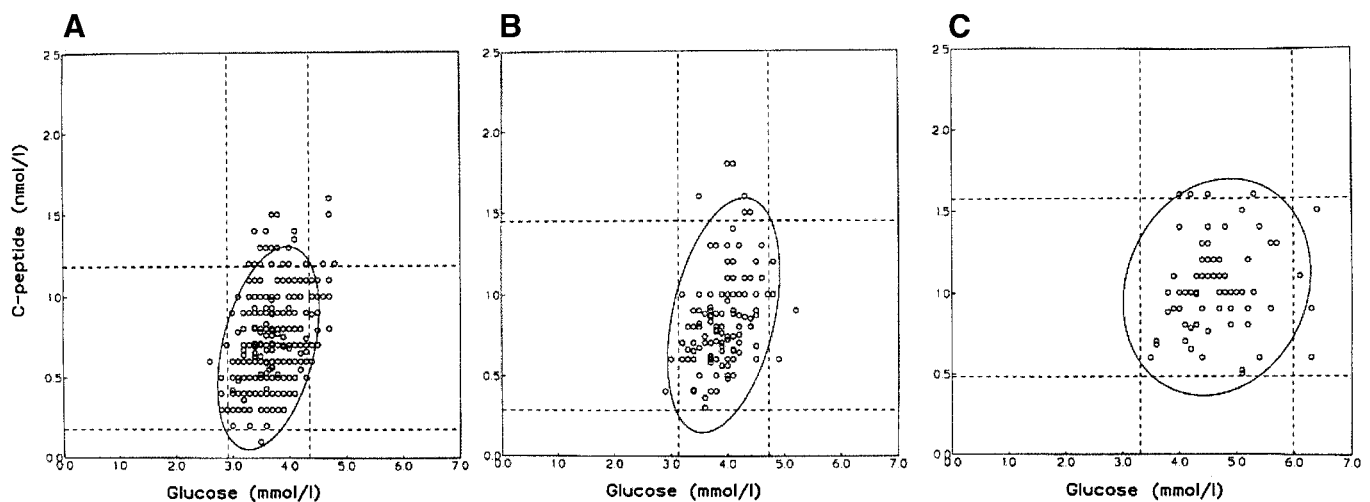


Figure 2—Plot of fasting glucose and C-peptide with the calculated 95% normal reference ellipse of control (A), MGH (B), and GDM (C) women. The indicated square is the reference area used in the conventional way.

However, there was no association between MGH and ethnicity.

GDM affects 3–4% of pregnant women (19,20). In this study, we found a prevalence of 6.9%, likely due to the high rate of immigrants in the Amsterdam-East region (17).

Epidemiological studies have shown that the risk of adverse birth outcomes is strongly related to GDM (20–22). The results of the present study, i.e., fetal macrosomia and low Apgar scores at 5 min, are in keeping with the results reported in those studies. Our study largely confirms the results of previous studies addressing determinants of GDM. Maternal age (23–25), ethnicity (23–25), and prepregnancy BMI (23,24) were positively associated with GDM but not pregnancy-induced or prepregnancy hypertension (26). This study showed significantly higher serum C-peptide levels in GDM women than in MGH women and control subjects. In GDM women, the correlation between fasting glucose and C-peptide was almost lost and, in addition, the fasting C-peptide-to-glucose ratio was two times less than in control subjects. These findings suggest a higher level of insulin resistance in GDM compared with MGH women and are compatible with the concept that glucose intolerance in GDM is (partly) due to an impaired ability of β -cells to further increase insulin secretion in response to glucose (27,28). The fact that ethnicity is the only factor distinguishing MGH from GDM suggests that genetic or lifestyle factors are involved in this type of β -cell dysfunction.

Finally, it is noteworthy that a population-based survey performed in one of the four above-mentioned town boroughs showed that all immigrant subjects had a significantly higher risk for type 2 diabetes than Caucasian subjects and that a significant association was found between non-Caucasian origin and the occurrence of GDM (17).

There are a number of caveats to the data presented here. Firstly, patient selection in the current study design was based on referral to an outpatient clinic of obstetrics and gynecology. Because of the selection bias that may have been introduced by this, we feel caution is required in extrapolating data of the control group to the general population. In control women, however, ethnicity was quite similar when compared with the female inhabitants of the four town boroughs in

close proximity to the hospital. Also, in our study, the established ranges of BMI, fasting glucose, and C-peptide in control women support the data of previous reports that studied relatively small random samples of the general population (29,30). Therefore, the data presented here offer some evidence in favor of representativeness. Secondly, the causal relation between the significant determinants of MGH and GDM cannot be proven using cross-sectional data. The close association shown in our study suggests a causal relation that requires further study.

In summary, MGH is characterized both by insulin resistance and a near-normal pattern of glucose-triggered insulin release. Of the well-known independent determinants of GDM, only maternal age and prepregnancy BMI were associated with MGH. Thus, it appears that additional factors promoting loss of β -cell function distinguish MGH from GDM. One of these factors appears to be ethnicity.

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