Elevated Homocysteine as a Risk Factor for the Development of Diabetes in Women With a Previous History of Gestational Diabetes Mellitus

A 4-year prospective study

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OBJECTIVE — To investigate the potential use of the plasma homocysteine level as a predictor of diabetes in women with a previous history of gestational diabetes mellitus (GDM).

RESEARCH DESIGN AND METHODS — At 6 weeks' postpartum, baseline examination was performed in 177 GAD-negative subjects. Of these subjects, 7 who were diagnosed with diabetes at baseline were excluded from further evaluation, and 170 with normal or impaired glucose tolerance (IGT) at baseline were followed annually over 4 years. The follow-up examinations included 2-h 75-g oral glucose tolerance tests (OGTTs), lipid profiles, homocysteine levels, anthropometric measurements, history taking, diet, and lifestyle. During the OGTTs, insulin and glucose levels were assayed every 30 min. Plasma homocysteine levels were determined by ion-exchange chromatography.

RESULTS — Of the 170 women, 18 (10.6%) converted to diabetes during the 4-year follow-up period. Mean age, BMI, fasting insulin, and total cholesterol at baseline (6 weeks' postpartum test) were similar in the three study groups (i.e., normal, IGT, and diabetes). Fasting glucose levels, insulin-to-glucose ratios, and homocysteine levels were significantly higher in the diabetic group ($P < 0.05$). Higher glucose at the time of the diagnosis of GDM and higher homocysteine levels at baseline were independently associated with the onset of postpartum diabetes. These relationships were independent of age, BMI, and family history of diabetes.

CONCLUSIONS — This prospective study identified homocysteine level as a significant risk factor for development of diabetes in women with previous GDM.

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Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity first recognized in pregnancy (1). GDM may complicate as many as 3–8% of all pregnancies in North America (2). Although the reported prevalence of GDM seems to be slightly lower in Asian countries (3,4), adverse outcomes are very similar in these two regions. Furthermore, women with GDM are at increased risk of later development of type 2 diabetes (5). Studies in Western populations have found conversion rates from 3 to 38% within the 1st year postpartum (6–8). Although a limited number of such studies have been performed in Asian countries, studies in Hong Kong and Korea found a 20 and 38.3% prevalence, respectively, of impaired glucose metabolism in the early postpartum period (9,10).

More than 4 decades ago, Wilkerson, O'Sullivan, and Mahan (5,11) initiated studies on glucose intolerance during pregnancy in an effort to identify women at risk of subsequent development of diabetes. The following clinical characteristics are reported to be key risk factors for development of diabetes postpartum: insulin requirement during pregnancy, earlier diagnosis of GDM during pregnancy, family history of diabetes, recurrence of GDM, increasing parity, maternal age, prepregnancy obesity, weight gain during pregnancy, and a previous macrosomic infant (12,13). Metabolic factors that predict risk of diabetes after GDM have also been identified. A high fasting glucose level during pregnancy, impaired β-cell function, and the presence of islet cell antibodies are associated with the postpartum development of diabetes (10,14,15).

During the past 2 decades, hyperhomocysteinemia has emerged as a risk factor for cardiovascular diseases (16). Detrimental effects of homocysteine on endothelial function are well documented (17,18). In addition, high levels of plasma homocysteine are known to exert an adverse effect through a mechanism involving oxidative damage (18). However, its relationships to and role in the onset of diabetes are unclear. Meigs et al. (19) reported that hyperhomocysteinemia is associated with hyperinsulinemia, and they suggested that this may partially account for an increased risk of cardiovascular disease when associated with insulin resistance. Other studies have reported a negative correlation or no relation between homocysteine and the insulin level

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Abbreviations: AUC, area under the curve; GDM, gestational diabetes mellitus; HOMA, homeostasis model assessment; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; ROC, receiver operating characteristic.

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

or insulin resistance syndrome (20,21). To the best of our knowledge, no study has previously examined homocysteine levels as a risk factor for the development of diabetes. Therefore, in this prospective study, we investigated the relationship between homocysteine and the development of diabetes in women with a previous history of GDM.

RESEARCH DESIGN AND METHODS

— The study subjects were recruited at three university hospitals, in Seoul, Pusan, and Suwon, Korea, that used the same procedures for the detection and diagnosis of GDM. During 24–28 weeks of pregnancy, a 50-g glucose challenge test was performed, followed by 3-h oral glucose tolerance test (OGTT) if plasma glucose 1 h later was ≥7.2 mmol/l. National Diabetes Data Group criteria were used to diagnose GDM (22). From August 1995 to May 1997, 275 subjects were recruited during pregnancy for a follow-up study. Subjects with one or more of the following were excluded from analysis: GDM during a previous pregnancy; positive for GAD antibody; a medical condition that might influence the homocysteine level (e.g., chronic renal failure, hypothyroidism, a history of breast or ovarian cancer); taking any of vitamin B_{12}, folate, metformin, fibrate, methotrexate, phenytoin, or theophylline; and current and ex-smokers (16,23). All subjects provided informed consent. The study protocol was approved by the ethical committee of the institutional review board of Ajou University School of Medicine.

Of the initial 275 subjects, 177 were eligible to participate in the postpartum follow-up analysis. Examinations were performed at baseline (6 weeks' postpartum) and annually thereafter. At baseline and follow-up examination, study subjects were stratified into three groups by 75-g OGTT based on 1998 World Health Organization classification (24): normal glucose tolerance (NGT), defined as fasting plasma glucose <7.0 mmol/l (126 mg/dl) and 2-h post glucose load <7.8 mmol/l (140 mg/dl); impaired glucose tolerance (IGT), defined as fasting plasma glucose <7.0 mmol/l (126 mg/dl) and 2-h post glucose load ≥7.8 to <11.1 mmol/l (140 to ~200 mg/dl); and diabetes, defined as fasting plasma glucose ≥7.0 mmol/l (126 mg/dl) or 2-h post glucose load ≥11.1 mmol/l (200 mg/dl), or both. We did not include impaired fasting glucose as a separate category. When an individual met criteria for the diagnosis of diabetes, she was regarded as an event. Subjects with normal or IGT were followed up continuously. Seven subjects with diabetes at the initial postpartum test were excluded from further follow-up testing.

At baseline and annual follow-up evaluations, lifestyle, dietary intake, family history of diseases, medical histories, and educational levels were determined for all participants by trained interviewers using a standardized questionnaire. A face-to-face interview method was used.

Anthropometric assessments and blood pressure measurement

To calculate BMI, height and weight measurements were taken barefoot in light clothing. Body fat percent was measured using a bioelectrical impedance method (body composition analyzer; Giru, Seoul, Korea). After subjects remained supine for 10 min, blood pressure measurements were taken three times with a 5-min rest period between measurements.

Laboratory assessments

Plasma glucose was measured using a glucose oxidase method (YSI 2300-STAT; Yellow Springs Instrument, Yellow Springs, OH) immediately after blood was drawn. Serum insulin was measured using radioimmunoassay kits (Linco Research, St. Louis, MO). Blood samples were sent to the central laboratory immediately for analysis of lipid profiles. Total cholesterol and triglyceride concentrations were determined enzymatically using a Beckman analyzer (Beckman Instruments, Brea, CA). HDL cholesterol levels were determined using a Sigma direct EZ-HDL assay. LDL cholesterol was calculated from total cholesterol, triglycerides, and HDL cholesterol results, using the Friedewald equation (25). GAD antibodies were measured by radioimmunoassay (RSR, Cardiff, Wales, U.K.). Creatinine clearance was estimated using the Cockroft-Gault formula (26). Plasma total homocysteine concentration was measured by ion-exchange chromatography using a modification of Anderson's method (27). The intra-assay coefficient of variation of this method is 5.3%.

Mathematical models

Various mathematical models were applied, and areas under the curves (AUCs) for glucose and insulin were calculated using the trapezoidal method. Using the fasting insulin and glucose values obtained from the OGTTs, pancreatic β-cell function, insulin resistance, and insulin sensitivity were calculated using the homeostasis model assessment (HOMA), HOMA2, and QUICKI (quantitative insulin-sensitivity check index) models (28–30).

Statistical analysis

Statistical analyses were conducted using SPSS for Windows version 11.0 (SPSS, Chicago, IL). Data are the means ± SD. Significant differences between groups were evaluated using the *t* test and the χ^2 test. Differences were considered statistically significant at $P < 0.05$. The contribution of homocysteine to development of diabetes was evaluated using a survival curve. The hazard ratios of potential risk factors were determined using the Cox proportional hazard model, with postpartum diabetes status as the dependent variable and various factors related with GDM, including homocysteine, as independent variables.

RESULTS

— During the 4-year postpartum follow-up (mean duration 2.94 ± 1.18 years), 18 of 170 participants (10.6%) converted to diabetes. Of these 18 subjects, 9 had NGT and 9 IGT at baseline. At the last examination, 43 of the 170 subjects (25.3%) had IGT (20 NGT and 23 IGT at baseline). Table 1 presents anthropometric and biomedical characteristics of the 170 subjects grouped according to their final glucose tolerance status at the end of follow-up. Comparisons are based on "prepregnancy" historical information and measurements that were made at the time of the OGTT that were diagnostic of GDM. The putative risk factors for postpartum diabetes (prepregnancy obesity, early diagnosis of GDM, and high glucose level) were more apparent in the subjects who later developed diabetes. The proportion of subjects requiring insulin treatment of GDM was larger in the diabetic group than in the other groups, with borderline significance. In terms of antepartum insulin and glucose responses after a 100-g OGTT, the highest glucose response occurred in the diabetic group, followed in order by the IGT and NGT groups. Conversely, insulin response was lowest in the diabetic group, followed in order by the IGT and NGT groups (data not shown).

Table 2 shows anthropometric and biomedical characteristics at baseline for the three groups according to their final classification (i.e., NGT, IGT, and diabe-

Table 1—*Historical information and anthropometric and metabolic findings at diagnosis of GDM in subjects grouped according to status at last postpartum follow-up (NGT, IGT, or diabetic)*

	NGT	IGT	Diabetic	*P*†
n	109	43	18	—
Age (years)	30.6 ± 4.3	32.1 ± 3.7	30.0 ± 3.0	NS
Prepregnancy BMI (kg/m^2)	22.0 ± 3.3	22.4 ± 2.3	24.0 ± 3.2	A,B
Family history of diabetes	33.9%	30.2%	44.4%	NS
Family history of hypertension	40.4%	41.9%	16.7%	NS
Prepregnancy education ≥9 years	47.7%	48.8%	44.4%	NS
Prepregnancy regular exercise ≥3 times/week	31.2%	30.2%	36.0%	NS
Number of children ≥3	32.1%	55.8%	33.3%	NS
Weight gain from first prenatal visit to diagnosis of GDM	3.38 ± 1.83	3.18 ± 2.07	2.04 ± 2.06	A
Gestational age at the time of GDM diagnosis (weeks)	26.2 ± 3.0	26.8 ± 3.3	23.9 ± 4.6	A,B
Fasting glucose (mmol/l)*	4.8 ± 0.6	5.0 ± 0.6	5.8 ± 1.2	A,B
Fasting insulin (pmol/l)*	84.7 ± 38.9	86.8 ± 33.3	111.8 ± 27.1	A,B
AUC glucose (mmol/l per 3 h)*	25.8 ± 2.2	26.5 ± 3.0	29.4 ± 4.2	A,B
AUC insulin (pmol/l per 3 h)*	1,104.3 ± 972.3	1,002.9 ± 946.6	645.9 ± 175.7	NS
1-h insulin (pmol/l)/glucose (mmol/l) increment*	64.1 ± 83.7	46.0 ± 60.5	40.9 ± 72.6	NS
Fasting insulin/glucose*	17.6 ± 70.1	17.3 ± 54.6	19.3 ± 22.8	A,B
HOMA of insulin resistance*	2.7 ± 1.3	2.8 ± 1.1	4.2 ± 1.6	A,B
HOMA2%B*	138.5 ± 50.1	136.0 ± 46.8	124.2 ± 34.2	NS
HOMA2%S*	91.6 ± 67.6	78.0 ± 45.1	53.0 ± 27.6	A
QUICKI*	0.34 ± 0.04	0.33 ± 0.03	0.31 ± 0.02	A,B
Insulin treatment for GDM	20.8%	21.4%	47.1%	0.056

Data are means ± SD unless otherwise indicated. Weight gain from first prenatal visit to diagnosis of GDM = mean difference between first prenatal visit and OGTT. *Values of fasting glucose and insulin measured at the time of GDM diagnosis were used; †ANOVA with post hoc test was used (A, B, and C mean significant difference between two groups: A = diabetes vs. NGT, B = diabetes vs. IGT, C = IGT vs. NGT, $P < 0.05$ in all cases) and χ^2 test for categorical data. HOMA2%B, percent β-cell function calculated using the HOMA2 computer model; HOMA2%S, percent insulin sensitivity calculated using the HOMA2 computer model; QUICKI, quantitative insulin sensitivity check index.

tes). Fasting glucose and homocysteine levels were significantly higher in the subsequently diabetic group than in the IGT or NGT groups ($P < 0.05$). The insulin-to-glucose ratio and β-cell function determined by HOMA2 were significantly lower in the diabetes group than in the NGT group ($P < 0.05$).

In the correlation analysis, there was a positive correlation between the last follow-up homocysteine level and fasting insulin levels in the diabetic and IGT groups ($r = 0.424$, $P = 0.007$). We performed additional analyses of the relationships between the homocysteine level and postpartum diabetes. Using the optimal cutoff point of the homocysteine levels at baseline by receiver operating characteristic (ROC) analysis, high (>6.38 mmol/l) or low (<6.38 mmol/l) Kaplan-Meier survival analysis was performed. Subjects with a high homocysteine level at baseline had a diabetes-free survival rate of 73.0% at 4 years postpartum, whereas the low group had a 93.7% diabetes-free survival rate. Using the Cox proportional hazard model, we investigated the independent risk of homocysteine level at baseline for the onset of diabetes during the postpartum follow-up (Table 3). In the model, we included those variables found to have a significant impact on the onset of diabetes after GDM (6,13,14,31): older age (>30 years), prepregnant BMI >23 kg/m^2, a family history of diabetes, fasting glucose level at the time of GDM diagnosis >5.3 mmol/l, and gestational age at diagnosis of GDM <26 weeks. The cutoff values for gestational age at diagnosis of GDM, fasting glucose at diagnosis of GDM (5.3 mmol/l), and homocysteine level at baseline (6.38 mmol/l) were obtained by ROC analyses. Furthermore, when the ROC analysis was made for each of the variables, fasting glucose at diagnosis of GDM had a higher area under the ROC curve value than homocysteine level at baseline, and gestational age at diagnosis of GDM had the lowest value. Consequently, fasting glucose level at diagnosis of GDM was the best predictor for future diabetes. High homocysteine level (>6.38 mmol/l) at baseline also had relatively high sensitivity and specificity (Table 4). Of these putative variables, we found that high fasting glucose level at the time of GDM diagnosis and high homocysteine level at baseline were independently and significantly associated with the onset of diabetes during the 4-year postpartum period, and early diagnosis of GDM during pregnancy showed borderline significance (Table 3). Those subjects with a fasting plasma glucose value >5.3 mmol/l had a four times (95% CI 1.4–11.4) higher risk of developing diabetes during the postpartum period than those with values <5.3 mmol/l. When those subjects who converted to diabetes at the early postpartum test (within 6 weeks) were included in the analysis, the hazard ratio for a high glucose level increased from 4.0 to 6.0 ($P < 0.001$). Those subjects who had a higher homocysteine level at baseline showed a 3.6 times (95% CI 1.06–11.9) higher risk of developing diabetes during the 4 years of follow-up than subjects with a lower homocysteine level.

CONCLUSIONS — In this 4-year prospective study, we identified three key risk factors for the onset of diabetes after GDM: high fasting glucose level at the time of GDM diagnosis, high homocys-

Table 2—*Comparison of anthropometric and biomedical characteristics at baseline (6 weeks' postpartum) according to the last glucose metabolism status*

Variables	NGT	IGT	Diabetic	P*
n	109	43	18	—
BMI (kg/m^2)	23.5 ± 3.2	23.8 ± 2.0	24.4 ± 2.9	NS
Fat (%)	30.4 ± 4.3	31.1 ± 5.4	30.0 ± 5.0	NS
Systolic blood pressure (mmHg)	110.0 ± 11.3	108.7 ± 11.1	115.4 ± 10.4	B
Diastolic blood pressure (mmHg)	69.5 ± 9.0	69.8 ± 8.7	73.5 ± 7.5	NS
Fasting glucose (mmol/l)	5.0 ± 0.5	5.3 ± 0.5	5.6 ± 0.8	A,B
Fasting insulin (pmol/l)	57.6 ± 25.0	56.9 ± 18.8	57.6 ± 22.2	NS
AUC glucose (mmol/l per 2 h)	22.6 ± 4.0	25.4 ± 4.4	27.1 ± 5.6	A,C
AUC insulin (pmol/l per 2 h)	706.3 ± 388.2	693.8 ± 315.3	670.2 ± 502.1	NS
Insulin/glucose	11.4 ± 4.7	10.8 ± 3.2	10.3 ± 3.9	A,B
ΔInsulin/Δglucose	65.3 ± 43.7	53.6 ± 34.0	37.4 ± 28.1	A
HOMA of insulin resistance	1.9 ± 0.9	1.9 ± 0.8	2.1 ± 0.9	NS
HOMA2%B	98.6 ± 30.5	89.6 ± 19.8	81.2 ± 26.6	A
HOMA2%S	115.1 ± 63.0	108.4 ± 53.2	111.7 ± 63.8	NS
QUICKI	0.36 ± 0.03	0.35 ± 0.03	0.35 ± 0.03	NS
HbA_{1c} (%)	5.2 ± 0.5	5.3 ± 0.4	5.4 ± 0.4	NS
Total cholesterol (mmol/l)	5.4 ± 0.9	5.7 ± 0.8	5.7 ± 1.0	NS
Triglyceride (mmol/l)	3.0 ± 1.7	4.6 ± 3.1	4.4 ± 2.4	A
HDL cholesterol (mmol/l)	1.5 ± 0.4	1.4 ± 0.4	1.6 ± 0.4	B
LDL cholesterol (mmol/l)	3.3 ± 0.8	3.3 ± 0.9	3.2 ± 0.9	NS
Homocysteine (mmol/l)	6.1 (5.8–6.5)	5.9 (5.4–6.5)	7.4 (6.4–8.3)	A,B

Data are means ± SE or geometric mean (95% CI). *ANOVA with post hoc test was used (A, B, and C mean significant difference between two groups: A = diabetes vs. NGT, B = diabetes vs. IGT, C = IGT vs. NGT, $P < 0.05$ in all cases). ΔInsulin/Δglucose = (30-min insulin − fasting insulin)/(30-min glucose − fasting glucose); QUICKI, quantitative insulin sensitivity check index; HOMA2%B, percent β-cell function calculated using the HOMA2 computer model; HOMA2%S, percent insulin sensitivity calculated using the HOMA2 computer model; LDL cholesterol = total cholesterol − (HDL cholesterol + triglyceride/2.2).

teine level in the early postpartum period, and early diagnosis of GDM. Of these, high glucose level during pregnancy is the best predictor of postpartum diabetes. This finding is consistent with studies conducted in other ethnic groups (14,31). Moreover, when those subjects who converted to diabetes within 6 weeks' postpartum were included in the analysis, high glucose level at pregnancy had a higher impact on development of diabetes. Thus, the strong association between high glucose level during pregnancy and the postpartum onset of diabetes may reflect a marked deterioration in maternal hyperglycemia in a subset of women whose hyperglycemia persisted postpartum.

The association between postpartum diabetes and early gestational age at GDM diagnosis has also been reported in previous studies (7,14). Furthermore, our study revealed that diabetic subjects had higher glucose and lower insulin responses during the antepartum period compared with the IGT and NGT groups. Although the lower AUC for insulin in the diabetic group was not statistically significant, the trend is similar to findings of a previous report (14) indicating that subjects destined to manifest early postpartum diabetes were relatively insulinopenic throughout pregnancy. These findings show that impaired insulin response had already manifested during pregnancy in the diabetic group and that this reduced response continued throughout the follow-up period. These results suggest heterogeneity of insulin response in the three groups (i.e., the subjects who converted to diabetes had been insulinopenic during pregnancy). In contrast, those who were classified as IGT or NGT showed relatively lower glucose and higher insulin response during pregnancy. This fact supports the appropriateness of our study design, specifically, by defining diabetes as an event in the survival analysis.

In this study, we found that high homocysteine level in the early postpartum period is an additional prognostic factor for postpartum diabetes, and that it has the same weighting as high fasting glucose level. In general, hyperhomocysteinemia

Table 3—*Cox proportional hazard model to identify risk factors for diabetes development after GDM*

Variables	β	SE	P	RR	95% CI of RR
Age >30 years	0.708	0.556	0.203	2.030	0.682–6.03
Gestational age at diagnosis of GDM <26 weeks	0.875	0.514	0.089	2.399	0.875–6.577
Prepregnancy BMI >23 kg/m^2	−0.250	0.540	0.644	0.779	0.270–2.246
Positive family history of diabetes	0.534	0.502	0.287	1.706	0.638–4.566
Higher fasting glucose level at diagnosis of GDM (>5.3 mmol/l)	1.387	0.534	0.009	4.004	1.405–11.409
Higher homocysteine level at baseline (6 weeks' postpartum [>6.38 mmol/l])	1.268	0.618	0.040	3.555	1.059–11.934

RR, relative risk.

Table 4—*Sensitivity, specificity, and positive and negative predictive value of the variables found to be significantly related to diabetes*

Variables	Sensitivity	Specificity	Predictive value		Area under the ROC curve
			Positive	Negative	
Gestational age at diagnosis of GDM <26 weeks	0.611	0.560	0.142	0.923	0.657
Higher fasting glucose level at diagnosis of GDM (>5.3 mmol/l)	0.667	0.783	0.267	0.952	0.809
Higher homocysteine level at baseline (6 weeks' postpartum [>6.38 mmol/l])	0.778	0.632	0.200	0.960	0.707

is a well-known risk factor for cardiovascular disease in both normal and diabetic subjects (16); however, few studies have investigated the relationship between homocysteine level and diabetes, and their results are inconsistent. Several studies have reported a higher level of homocysteine in patients with type 1 or type 2 diabetes than in normal subjects (32,33). Furthermore, a European study reported an independent association between homocysteine level and glucose utilization (determined with a hyperinsulinemic-euglycemic clamp) (34). However, it is unclear whether hyperhomocysteinemia precedes the development of diabetes or results from it. We observed a positive correlation between homocysteine level and fasting insulin concentration in our insulin-resistant diabetic and IGT subjects with high levels of insulin. These findings are consistent with those of others (19,35). However, this pattern would not be expected with more severe insulin deficiency or in type 1 diabetes. In a streptozotocin rat model of diabetes, insulin has been shown to have a direct role in regulating the metabolism of homocysteine. The level of hepatic cystathionine β-synthase, a transmethylation enzyme that metabolizes conversion of homocysteine to cystathione (36), was elevated and plasma homocysteine reduced in untreated, insulin-deficient diabetic rats, and the defects were normalized by treatment with insulin. Furthermore, cystathionine β-synthase mRNA levels were markedly elevated in streptozotocin-induced diabetic rat livers and reduced by insulin administration (37). Considering that insulin resistance may be an expression of diffuse arterial endothelial dysfunction, which contributes to atherosclerosis directly or indirectly (38), it is not surprising that these two risk factors are associated with cardiovascular disease. Furthermore, we observed a positive correlation between the baseline homocysteine level and AUC glucose at the time of GDM diagnosis. We did not measure homocysteine when the diagnosis of GDM was made, but, based on this correlation, one can speculate that homocysteine was also elevated during pregnancy in those with the most severe glucose intolerance, who are also at highest risk for postpartum diabetes.

The limitations of this study is the lack of folate or vitamin B_{12} values, which are directly or indirectly associated with homocysteine level (39). However, subjects who had taken vitamins or folate were excluded, and thus their effect on homocysteine level should be limited. Although homocysteine levels could be influenced by mutation frequencies of the methylenetetrahydrofolate reductase gene, the main methylenetetrahydrofolate reductase polymorphism is not associated with increased maternal homocysteine during pregnancy (40) or with homocysteine levels in Koreans in general (41). Therefore, it appears unlikely that this mutation could have influenced our results.

This is the first prospective study that has attempted to determine the association between homocysteine and the onset of diabetes in women with previous GDM. Our results suggest that early postpartum hyperhomocysteinemia in a GDM mother is another risk factor for the development of diabetes during the postpartum period. Thus, the measurement of homocysteine level at 6 weeks' postpartum would be helpful to identify women with a previous history of GDM at high risk of developing diabetes. Finally, our study underscores the need to assess the metabolic effects of elevated plasma homocysteine levels beyond the detrimental effects on the vascular endothelium.

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