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ORIGINAL ARTICLE

Heterogeneity of maternal characteristics and impact on gestational diabetes (GDM) risk—Implications for universal GDM screening?

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ABSTRACT

Objective To study the incidence of gestational diabetes mellitus (GDM) in relation to phenotypic characteristics and gestational weight gain (GWG) among women at high risk for GDM.

Materials and methods This is a secondary analysis of a GDM prevention study (RADIEL), a randomized controlled trial conducted in Finland. 269 women with a history of GDM and/or a pre-pregnancy body mass index (BMI) ≥ 30 kg/m^2 were enrolled before 20 weeks of gestation and divided into four groups according to parity, BMI and previous history of GDM. The main outcome was incidence of GDM.

Results There was a significant difference in incidence of GDM between the groups ($p < 0.001$). Women with a history of GDM and BMI <30 kg/m^2 showed the highest incidence (35.9%). At baseline they had fewer metabolic risk factors and by the second trimester they gained more weight. There was no interaction between GWG and GDM outcome and no significant difference in the prevalence of diabetes-associated antibodies.

Conclusion Despite a healthier metabolic profile at baseline the non-obese women with a history of GDM displayed a markedly higher cumulative incidence of GDM. GWG and the presence of diabetes-associated antibodies were not associated with GDM occurrence among these high-risk women.

KEY MESSAGE

- Despite a healthier metabolic profile at baseline the non-obese women with previous gestational diabetes mellitus display a markedly higher cumulative incidence of gestational diabetes mellitus.

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Diabetes-related autoantibodies; gestational diabetes; gestational weight gain; heterogeneity; lifestyle interventions; obesity; screening; type 2 diabetes

Introduction

The incidence of gestational diabetes mellitus (GDM) is increasing worldwide (1–3). The prevalence of GDM among pregnant women is 2–18% globally (2–4) and around 14% in Finland (5). The prevalence of overweight and obesity, well known risk factors for GDM, among women who gave birth 2012–2013 in Finland was 35% according to recently published data (5). The documentation of unfavorable consequences of GDM and overweight is solid, showing long-term health consequences for both the mother and the offspring (4,6,7) and forming a great incentive to search for efficient GDM

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prevention methods. Several interventions targeting GDM prevention have been undertaken but the results have been inconsistent (8–11).

The heterogeneity of type 2 diabetes is well known and has been the focus of several previous studies (12). In contrast, there has been little focus on the heterogeneity of GDM. Some studies have found differences in insulin sensitivity, insulin secretion, body composition, and occurrence of autoantibodies (13,14) among women with GDM. Previous studies of glutamic acid decarboxylase antibody (GADA) and islet cell antibody (ICA) prevalence in GDM women have mainly focused on their predictive value regarding postpartum risk of type 1 diabetes (15). However, the clinical significance of type 1 diabetes-related autoantibodies in relation to the incidence of GDM remains unclear. Consequently, the heterogeneity of GDM has not been taken into account when planning strategies for GDM prevention or in previous GDM prevention trials.

The purpose of the present study was to focus upon clinical characteristics of women at high risk for GDM. This may help to optimize individualized GDM prevention strategies in the future.

Materials and methods

Study design

This study is a secondary analysis of data collected in the Finnish Gestational Diabetes Prevention Study (RADIEL), a multicenter randomized controlled intervention trial targeting women at high risk for GDM. The RADIEL study was conducted in Finland between February 2008 and January 2014 in all three maternity hospitals of the Helsinki metropolitan area (Helsinki University Hospital (HUH), Department of Obstetrics and Gynecology; Kätilöopisto Maternity Hospital; Jorvi Hospital) and in the South-Karelia Central Hospital (SKCH) in Lappeenranta.

Participants

Eligible persons for the RADIEL study were pregnant women over 18 years of age with a history of previous GDM or a pre-pregnancy body mass index (BMI) ≥ 30 kg/m^2, or both, at less than 20 weeks of gestation. Overt GDM or diabetes at enrollment were exclusion criteria, as well as multiple pregnancy, physical disability, current substance abuse, severe psychiatric disorders, difficulties in co-operation, and regular medication influencing glucose metabolism. The total number of pregnant women included was 269. The study protocol was approved by the Ethics Committees of HUH and SKCH, and registered at clinicaltrials.gov (IDr: NCT01698385). All participants provided written informed consent. The design and the main results of the RADIEL intervention trial have been presented elsewhere (8).

Table 1. Group characteristics.

	Group			
	A N = 113	B N = 68	C N = 64	D N = 24
BMI ≥ 30 kg/m^2	+	+	−	+
Previous pregnancies	−	+	+	+
Previous history of GDM	.	−	+	+

For the analyses of this study, we divided the RADIEL study participants into four groups according to parity, BMI, and previous history of GDM (Table 1).

Outcomes

The primary endpoint was the incidence of GDM, defined as one or more pathological glucose values in a 75 g two-hour oral glucose tolerance test (OGTT) with the following diagnostic thresholds: fasting plasma glucose ≥ 5.3 mmol/L, one hour value ≥ 10.0 mmol/L, and two hour value ≥ 8.6 mmol/L. The OGTT was performed at the time of enrollment and repeated at 24–28 weeks of gestation.

Gestational weight gain (GWG) was obtained by calculating the change between the self-reported pre-pregnancy weight and the weight in the second trimester visit at 23.1 (median, IQR 22.4–24.1) weeks of gestation.

The food frequency questionnaire and the dietary index designed for the RADIEL study have been described previously (8). The dietary index is based on 11 food components in accordance with the National Dietary Guidelines and scored according to reported frequency of intake with higher scores indicating higher diet quality. Evaluation of leisure-time physical activity was based on self-reported time spent on physical activity per week. Diet and physical activity were assessed in each trimester.

The study participants were also asked about their chronic illnesses including asthma, cardiovascular diseases, gastrointestinal diseases, neurological diseases, endocrinological diseases and psychiatric disorders.

Blood pressure was measured from the right arm while the subject was in the sitting position using a sphygmomanometer.

Venous blood samples were taken in a sitting position with a light stasis into a serum gel tube and were centrifuged at the survey sites. Laboratory tests performed in conjunction with the study visits included measurements of fasting plasma glucose (fP-Gluk) and

Table 2. Demographic and clinical characteristics at baseline (first trimester) for groups A, B, C and D.

	Group A N = 113	Group B N = 68	Group C N = 64	Group D N = 24	p value between groups (multiple comparison)*
Age (years), mean ± SD	30 ± 5	33 ± 5	33 ± 4	33 ± 5	<0.001 (A/B, A/C, A/D)
BMI (kg/m^2), mean ± SD	34.2 ± 3·8	34.2 ± 3·6	23.6 ± 2·7	34.7 ± 4.3	<0.001 (A/C, B/C, C/D)
Years of education, mean ± SD	14.1 ± 2.6	13.6 ± 2.4	14.8 ± 2.4	13.1 ± 2.6	0.028 (C/D)
Parents' history of diabetes, n (%)	24 (21)	11 (18)	15 (24)	7 (30)	0.61
Previous deliveries, n (%)					<0.001 (B/C, B/D)
1	–	48 (71)	25 (39)	7 (29)	
2	–	14 (21)	29 (45)	10 (42)	
≥3	–	6 (9)	10 (16)	7 (29)	
Dietary index score, mean ± SD	9.57 ± 2.60	9.46 ± 2.85	10.69 ± 2.74	10.86 ± 2.71	0.011 (A/C)
Physical activity (minutes), median (IQR)	60 (30, 125)	60 (30, 140)	90 (45, 150)	60 (0, 180)	0.65

Continuous data are presented as mean values (standard deviation, SD). Group A: primiparous, BMI ≥ 30 kg/m^2. Group B: multiparous, no previous GDM, BMI ≥ 30 kg/m^2. Group C: multiparous, previous GDM, BMI < 30 kg/m^2. Group D: multiparous, previous GDM, BMI ≥ 30 kg/m^2.
*Hommel's multiple comparison procedure was used to correct significance levels for post hoc testing ($p < 0.05$).

insulin (fP-Insu), glycated hemoglobin (GHbA1c), total cholesterol (fP-Kol), low-density lipoprotein (fP-Kol-LDL) and high-density lipoprotein (fP-Kol-HDL) cholesterol and triglycerides (fP-Trigly), adiponectin, interleukin-6 (IL-6), tumor necrosis factor (TNF-alpha), high-sensitive C-reactive protein (hsCRP) and 25-hydroxy vitamin D (25-OH-D).

Lipids, hs-CRP, insulin, and glucose measurements were performed in the Helsinki University Hospital laboratory (HUSLAB). The following methods were used: for fP-gluk enzymatic hexokinase assay (Roche Diagnostics, Gluco-quant, Modular analyser), for fP-Insu electrochemiluminescence immunoassay (ECLIA) (Roche Diagnostics, Insulin, Modular analyser), for GHbA1c immunoturbidimetric analyser (Roche Diagnostics, Tina-quant Hemoglobin A1C Gen.2Integra800 analyser), for fP-Kol enzymatic assay (Roche Diagnostics, Cholesterol CHOD-PAP, Modular analyser), for fP-Kol-LDL enzymatic assay (Roche Diagnostics, LDL-C plus 2nd generation, Modular analyser), for fP-Kol-HDL enzymatic assay (Roche Diagnostics, HDL-C plus 3rd generation, Modular analyser), for fP-Trigly enzymatic assay (Roche Diagnostics TG Triglycerides GPO-PAP, Modular analyser) and for hs-CRP High sensitive assay, Immunoturbidimetric latex enhanced assay (Roche Diagnostics, CRPHS Tina-Quant Cardiac C-reactive protein (Latex) Modular analyser).

The 25-OH-D concentration was analyzed by a chemiluminescence method with commercial IDS-iSYS 25-Hydroxy Vitamin D-assay (Immunodiagnostic Systems Ltd, UK, Boldon). High molecular weight (HMW) adiponectin was determined by enzyme linked immunosorbent assay (human HMW) Adiponectin ELISA (Millipore, Billerica, MA). IL-6 and TNF-alpha were measured by multiplex sandwich immunoassay (Milliplex High Sensitivity Human Cytokine kit, Millipore).

Islet cell antibodies (ICA) and antibodies to GAD were analyzed as previously described (16). The limit value for ICA positivity was 2.5 Juvenile Diabetes Foundation units (JDFU). The limit value for GADA positivity was 5.36 relative units (RU) according to the 99th percentile in 372 non-diabetic Finnish subjects (17). The disease sensitivity and specificity of the ICA assay were 100 and 98%, and of the GADA assay 79 and 97%, respectively. The insulin resistance index (HOMA-IR) was calculated as (FPI (mU/l) × FPG (mmol/l))/22.5 and the index for beta cell function (HOMA-β) by (20 × FPI (mU/l))/((FPG (mmol/l) − 3.5).

Statistical analysis

The data are presented as means with standard deviations (SD), as medians with interquartile range (IQR), or as counts with percentages. Between-group comparisons were made using analysis of variance (ANOVA) and the Kruskal–Wallis test for continuous variables; and using Chi-squared tests for categorical variables. The p values for pairwise group comparisons were adjusted for multiplicity using Hommel's multiple comparison procedure to identify significant differences in at least one of the two between-group comparisons ($p < 0.05$). The p values for pairwise group comparisons in GDM outcome were adjusted for multiplicity using Hochberg's multiple comparison procedure. Logistic regression was used to model the occurrence of GDM using as second trimester physical activity and dietary score, age, years of education and family history of diabetes as covariates. Analysis of covariance (ANCOVA) was used to compare the groups as weight gain taking physical activity in second trimester and diet score in second trimester, age, years of education and family history of diabetes as covariates. In the case of violation of the assumptions (e.g. non-normality), a bootstrap-type test was used (10,000 replications). The normality of the variables was tested using the Shapiro–Wilk *W* test. All analyses were performed using STATA software (version 14.0) (StataCorp, LP, TX).

Table 3. Laboratory test values and blood pressure at baseline (first trimester) for groups A, B, C and D.

	Group A, N = 113	Group B, N = 68	Group C, N = 64	Group D, N = 24	p value between groups (multiple comparison)*
Fasting plasma glucose (mmol/L)	4.85 ± 0.24	4.89 ± 0.24	4.89 ± 0.26	4.92 ± 0.20	0.49
Insulin (mU/L)	10.39 ± 8.42	8.82 ± 3.58	5.01 ± 2.48	7.90 ± 3.01	<0.001 (A/C, B/C, C/D)
HbA_{1c} (%)	5.2 ± 0.25	5.2 ± 0.31	5.2 ± 0.27	5.2 ± 0.27	0.27
HbA_{1c} (mmol/mol)	32.9 ± 2.7	33.8 ± 3.4	33.7 ± 3.0	33.3 ± 3.0	0.27
HOMA-IR	2.27 ± 1.88	1.87 ± 0.79	1.09 ± 0.58	1.74 ± 0.74	<0.001 (A/C, B/C, C/D)
HOMA-β	124 (92, 168)	129 (91, 178)	63 (48, 76)	103 (84, 133)	<0.001 (A/C, A/D, B/C, C/D)
Total cholesterol (mmol/L)	4.82 ± 0.73	5.11 ± 0.94	4.71 ± 0.91	5.57 ± 0.96	<0.001 (A/D, C/D)
LDL cholesterol (mmol/L)	2.73 ± 0.60	3.00 ± 0.86	2.60 ± 0.70	3.22 ± 0.81	<0.001 (A/D, B/C, C/D)
HDL cholesterol (mmol/L)	1.67 ± 0.31	1.76 ± 0.31	1.80 ± 0.33	1.84 ± 0.30	0.013 (A/C)
Total triglycerides (mmol/L)	1.38 ± 0.54	1.35 ± 0.48	1.11 ± 0.42	1.81 ± 1.33	<0.001 (A/C, B/C, C/D)
hs-CRP (mmol/L)	9.0 ± 6.5	8.0 ± 5.4	4.0 ± 4.3	13.7 ± 13.0	<0.001 (A/C, B/C C/D)
TNF (pg/mL)	11.5 ± 10.1	11.0 ± 5.7	12.7 ± 10.8	10.8 ± 5.9	0.73
IL-6 (pg/mL)	6.2 ± 7.4	5.5 ± 6.0	9.5 ± 15.6	5.9 ± 4.2	0.29
Adiponectin (mg/mL)	16.9 ± 6.0	16.8 ± 5.5	19.9 ± 7.1	16.5 ± 5.8	0.028 (A/C, B/C)
25-OH-vitamin D (nmol/L)	57.6 ± 20.9	60.9 ± 23.6	63.4 ± 20.0	58.8 ± 23.0	0.43
Blood pressure					
Systolic (mmHg)	123 ± 13	123 ± 12	115 ± 11	132 ± 13	<0.001 (A/C, A/D, B/C, B/D, C/D)
Diastolic (mmHg)	79 ± 9	78 ± 8	72 ± 8	82 ± 10	<0.001 (A/C, B/C, C/D)
GAD Ab > 5.35 RU, n (%)	2 (2)	1 (1)	1 (2)	1 (4)	0.75
ICA > 2.5 JDFU, n (%)	5 (5)	3 (4)	2 (3)	1 (4)	0.98

Continuous data are presented as mean values (standard deviation, SD), HOMA-β median (IQR). Group A: primiparous, BMI $\geq$ 30 kg/m^2. Group B: multiparous, no previous GDM, BMI $\geq$ 30 kg/m^2. Group C: multiparous, previous GDM, BMI < 30 kg/m^2. Group D: multiparous, previous GDM, BMI $\geq$ 30 kg/m^2.
*Hommel's multiple comparison procedure was used to correct significance levels for post hoc testing ($p < 0.05$).

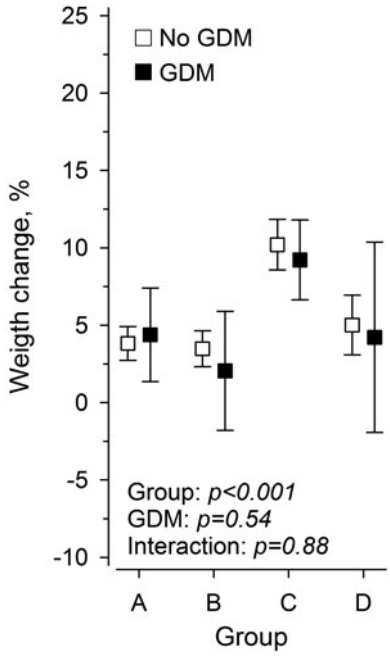

Figure 1. Gestational weight gain according to group and GDM outcome. Adjusted for physical activity in second trimester and diet score in second trimester, age, years of education and family history of diabetes. Group A: primiparous, BMI $\geq$ 30 kg/m^2. Group B: multiparous, no previous GDM, BMI $\geq$30 kg/m^2. Group C: multiparous, previous GDM, BMI <30 kg/m^2. Group D: multiparous, previous GDM, BMI $\geq$ 30 kg/m^2.

Results

Table 2 shows demographic and clinical characteristics of the study participants according to parity, previous history of GDM, and BMI. The prevalence of chronic diseases was 25% (n = 66), most common being asthma, and there was no significant difference between the groups.

The laboratory results and blood pressure levels at baseline, i.e. at median 13.3 gestational weeks (interquartile range [IQR] 12.0–14.6 weeks of gestation), are shown in Table 3 according to group. At baseline the women with previous GDM and BMI <30 kg/m^2 (group C) had lower fasting insulin concentrations, lower HOMA-IR, lower HOMA-β and lower hs-CRP. They also showed significantly higher adiponectin concentrations.

There was a significant difference in the occurrence of GDM between the groups. The occurrence in group A was 9.7%, in group B 11.8%, in group C 35.9%, and in group D 20.8% ($p < 0.001$, adjusted for second trimester physical activity and dietary score, age, years of education and family history of diabetes). After multiplicity adjustment GDM occurrence in group C was significantly higher when compared to groups A or B ($p < 0.001$), as well as when compared to group D ($p = 0.021$).

Between baseline and the follow-up at second trimester, there were differences in GWG between the groups. The mean GWG for group A was 3.7 kg, whereas it was 3.1 kg for group B, 6.3 kg for group C, and 4.5 kg for group D, respectively ($p < 0.001$). Since there were marked differences in baseline BMI of the participants, we analyzed GWG also as a percentage of pre-pregnancy weight according to group (Figure 1).

There was no significant difference in GWG between the non-diabetic women and the women diagnosed with GDM. This finding was similar in all groups as shown in Figure 1. There was no interaction between

GWG and GDM outcome. No significant difference was observed between the groups concerning the prevalence of diabetes-associated antibodies.

Conclusions

All women included in this study were at high risk for GDM. By subdividing the participants according to clinical characteristics, marked differences in the occurrence of GDM were noticed. Women with a pre-pregnancy BMI <30 kg/m^2 and a previous history of GDM were characterized by fewer metabolic risk factors at baseline compared with the other groups; they were more insulin sensitive and showed a healthier lipid profile. Despite the healthier metabolic profile at baseline, these women displayed a markedly higher cumulative incidence of GDM compared with the other groups.

The results of this study are not in accordance with previous studies displaying increasing risk for GDM with higher BMI (18) and more unfavorable metabolic profile (19). One possible explanation for this discrepancy could be the marked heterogeneity of GDM. Although obesity and overweight are known major risk factors for GDM, many previous studies have reported that genetic and autoimmune features add to this risk (13,14,20,21). For other forms of diabetes, the pathogenesis and its clinical importance have been extensively studied and presented as a result of a whole spectrum of different, partially overlapping, mechanisms (12). There are good reasons to believe that the diversity of GDM pathogenesis is of great clinical importance as well. At the moment there is a worldwide debate on the screening of GDM. Our results highlight the need for universal screening in accordance with the latest recommendations of IADPSG and ADA (year 2015), since there are also many individuals at high risk for GDM among non-obese women (22,23).

In previous studies, GADAs in GDM women have been associated with a lower BMI and lower insulin resistance during pregnancy (14). These autoantibodies are mainly associated with risk for type 1 diabetes. Hypothetically autoimmunity might partly explain the higher incidence of GDM observed in group C since none of the baseline clinical characteristics studied offered any explanation for this. However, the prevalence of GADAs in all groups was low (16) and there was no significant difference in GADA and ICA prevalence between the groups. Thus, the prevalence of diabetes-associated antibodies did not provide any explanation for the differences in GDM incidence.

Excessive GWG has been described as a risk factor for GDM (24–28). The women in group C differed from the other participants by gaining relatively more weight during follow-up. This finding was expected as normal-weight women are advised to gain more weight during pregnancy compared with obese women (29). However, we found no association between GWG and GDM occurrence in any of the groups. Hence, the higher level of GWG in group C does not offer an explanation for the higher GDM incidence.

The well-documented association of excessive GWG with GDM is generally considered as evidence that supports the possibility to prevent GDM by limiting GWG. The findings from studies assessing lifestyle intervention strategies for GDM prevention, on the other hand, have been inconsistent. Some studies have been successful in reducing GWG but the effect on GDM incidence has been minor or non-existing (9–11). However, according to our recently published RCT (8), a reduction of GDM incidence by a lifestyle intervention is both possible and feasible in women at high risk for GDM. The moderate-intensity physical activity and diet intervention implemented in the RADIEL study reduced the incidence of GDM by 39%.

We hypothesize that the described inconsistent study results might be explained at least partly by the lack of relationship between a modest GWG and GDM occurrence and by the heterogeneity of GDM, which is probably explained by different pathogenesis. It is possible that the compensatory insulin secretion is not achieved in normal weight women with GDM and therefore the pathogenesis in these women might not be based on insulin resistance but deficiency in secretion. Suggestive of this hypothesis is also the lower HOMA-β in group C at baseline. In randomized intervention trials the results might be largely influenced by the heterogeneity in the study populations. Potentially, to obtain a better outcome, the approach to GDM prevention and treatment needs to be modified according to the underlying pathophysiology.

The strength of this present study lies in its exceptional study design which also includes non-obese women at high GDM risk. To our knowledge, most GDM intervention trials have been focusing on obese or overweight women, and non-obese women with a previous history of GDM have been included in only one previous study (10). The pre-pregnancy weight and physical activity were self-reported in this study and can therefore be considered a weakness of the study. Since all the participants in this study are of white Caucasian origin, there are limitations on the generalizability of our findings to other ethnic populations than Caucasians. Several studies have shown different predisposition for GDM according to ethnic group (30). Our assumption is that the heterogeneity would only be more prominent

had this study been conducted in an ethnically more diverse population.

In conclusion, by separating the non-obese women with a history of GDM from the other participants, we obtained results pointing towards considerable heterogeneity among women with high GDM risk. This should be taken into account when planning GDM prevention strategies in the future. Since we have reported a surprisingly high occurrence of GDM in the group of non-obese women, the need for universal screening should be re-evaluated and it would also be of great importance to assess their future risk of type 2 diabetes.

Declaration of interest

None of the authors have any conflicts of interest to declare.

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