CLINICAL STUDY

Are short women at risk for gestational diabetes mellitus?

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Abstract

Objective: The aim of the study was to assess the influence of height variations on the risk of gestational diabetes mellitus (GDM).

Research design and methods: We analyzed the medical records of 1830 Caucasian women with GDM and 1011 healthy pregnant women. The following data were collected: age, prior macrosomia, prior GDM, parity, history of type 2 diabetes in first-degree relatives, weight before pregnancy, weight gain during pregnancy, glucose level at the first obstetric visit, results of the glucose challenge test and oral glucose tolerance test (OGTT), HbA1c, and method for treatment of GDM.

Results: Women with GDM were significantly shorter than the healthy controls (165.7 ± 5.6 cm vs 163.8 ± 6.6 cm; P < 0.001). The differences in height were not significant between GDM women who required insulin therapy and those treated with diet alone (P = 0.12). All the studied variables, including height, were independently associated with GDM. Even after adjustment for confounding variables, height was still associated with GDM (odds ratio 0.958, 95% confidence interval: 0.94–0.97; P < 0.00001). In women with GDM diagnosed by 75-g OGTT, we found a significant inverse association of height adjusted for age and pregravid weight with 2-h glucose level (β = −0.12; P < 0.0001).

Conclusions: Caucasian women with GDM are shorter than pregnant women without GDM regardless of the diagnostic criteria used or the severity of glucose intolerance. Although height is an independent predictor for GDM, its predictive value for identifying women at risk is relatively low and should not be considered in selective screening for this disease.

Introduction

In 1991, Brown et al. (1) published the first study demonstrating the negative relationship between height and glucose tolerance in adults. Further studies not only confirmed this observation in different ethnic groups with type 2 diabetes (2–5), but also showed that women with gestational diabetes mellitus (GDM) were usually shorter than women without GDM (6–12). This association between short stature and a higher prevalence of both type 2 diabetes and GDM were usually shorter than women without GDM (6–12). This association between short stature and a higher prevalence of both type 2 diabetes and GDM suggests that both forms of glucose intolerance are likely to have a similar pathogenesis characterized by insulin resistance and β-cell dysfunction (13, 14).

The higher prevalence of short stature in women with GDM was noted in both homogeneous (6, 7, 10) and heterogeneous (8, 9, 11, 12) racial groups, and there was a negative relationship between height and the severity of glucose intolerance. By comparing pregnant women with one abnormal result in the diagnostic oral glucose tolerance test (OGTT) with women diagnosed with either GDM or pregravid type 2 diabetes, Anastasiou et al. (6) showed a linear relationship between decreasing height and increasing frequencies of abnormal glucose tolerance and insulin resistance. Similarly, other studies demonstrated significant differences in height between healthy pregnant women, women with a false positive OGTT result, and women diagnosed with GDM (7). This direct link between short stature and increased risk for GDM might be clinically relevant, especially in screening strategies based on a selective approach that uses a history of traditional risk factors as a selection for screening. However, implementing these results in clinical practice in Caucasian women seems uncertain mostly due to methodological considerations. Previous studies were performed on either mixed (8, 9, 12) or non-Caucasian (6, 7, 10) populations. Therefore, their results may not apply to all populations due to the variations in average height between countries and socioeconomic groups (8, 9). The results may also be influenced by variations in the diagnostic methods that have been developed to identify women at risk of GDM. In Poland, GDM is routinely diagnosed using a glucose challenge test followed by a diagnostic 75-g OGTT according to the World Health Organization (WHO) criteria (15). Many more women with GDM are identified using the WHO criteria, and they have a wider range of blood glucose concentrations than those identified with the criteria recommended by the

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American Diabetes Association (ADA) (16). In general, women with GDM diagnosed using the ADA criteria have higher mean blood glucose concentrations during pregnancy than those diagnosed using the WHO criteria (15–17).

Given this diagnostic variation, we decided to test the following hypotheses: i) height might be a risk factor for abnormal glucose tolerance during pregnancy in a homogeneous group of Polish Caucasian women, and ii) height differences might predict the severity of abnormal glucose tolerance in women with GDM. Based on these assumptions, we also tested for the possibility to include height to the list of traditional risk factors used in selective screening for GDM.

Material and methods

In this retrospective study, we assessed the influence of height on the risk of GDM by analyzing the medical records of 1830 women with abnormal glucose challenge test who were referred to the Outpatient Clinic for Diabetic Pregnant Women in Szczecin (north–west Poland) from 1999 to 2005 (inclusive).

In Poland, as a routine procedure, GDM is diagnosed by a two-step approach using a glucose challenge test followed by a 75-g OGTT. The challenge test entails oral administration of 50 g of glucose at 24 to 28 weeks gestation, regardless of the length of time since the last meal, with a measurement of plasma glucose 1 h later. Women with 1-h glucose level > 180 mg/dl (10.0 mmol/l) in the challenge test were classified as having GDM. Women with plasma glucose concentrations between 140 mg/dl (7.8 mmol/l) and 180 mg/dl (10.0 mmol/l) were referred for a diagnostic 75-g OGTT. Based on the results of the diagnostic OGTT, GDM was diagnosed if either the fasting glucose level was ≥ 110 mg/dl (6.1 mmol/l) or the 2-h glucose concentration was ≥ 140 mg/dl (7.8 mmol/l), consistent with the WHO criteria (15). Additionally, we also used the diagnostic criteria for GDM recommended by the ADA (16), where at least two of the three following values were above the reference range: fasting glucose level ≥ 95 mg/dl (5.3 mmol/l), 1-h glucose level ≥ 180 mg/dl (10.0 mmol/l), and 2-h glucose level ≥ 155 mg/dl (8.6 mmol/l). Women with pregravid diabetes or multiple pregnancies were excluded from further analyses.

The control group consisted of 1011 healthy women with a single pregnancy and a normal challenge test. Women were considered healthy if they did not have a present or past history of medical conditions requiring treatment, declared no history of alcohol or narcotic abuse, and showed no abnormalities upon physical examination. The protocol was approved by the institutional review board.

The following data were collected for all women: age, prior macrosomia, prior GDM, parity, history of type 2 diabetes in first-degree relatives, weight before pregnancy, weight gain during pregnancy, glucose level at the first obstetric visit, results of the glucose challenge test and OGTT, HbA1c, and method for treatment of GDM. Body mass index (BMI) was calculated from the most recent weight (kg) before conception, and height (m) was measured with a single fixed stadiometer.

All women with GDM were educated and motivated by personnel trained in patient education. The patient education skills of the staff were reviewed, evaluated, and reinforced on a regular basis. Women were trained in achieving effective self-monitoring of their blood glucose levels by four daily measurements (fasting and 1 h after main meals) and self-adjustment of insulin dose in case of inadequate glycemic control. The treatment regimen included diet, insulin neural protamine hagedorn (NPH) given at bedtime, and/or short-acting human insulin before meals. The therapeutic goals were fasting blood glucose of 60–90 mg/dl (3.3–5.0 mmol/l) and blood glucose below 130 mg/dl (7.3 mmol/l) after meals. These goals were evaluated at each weekly visit.

Statistical analysis

The distribution of continuous variables was tested for normality by the Shapiro–Wilk test. Comparisons between groups for study variables were done using one-way ANOVA followed by post tests. Unpaired t-tests and χ² test were used to compare baseline characteristics between women with and without GDM. Univariate and multivariate logistic regression analyses were used to explore the associations between risk factors (age, height, BMI, family history of type 2 diabetes, prior macrosomia, and prior GDM) and a diagnosis of GDM. The results of the analyses are expressed as odds ratios (ORs) and 95% confidence intervals (CIs). For determination of a cut-off value for height, the coordinate of a receiver operating characteristic (ROC) curve was used. Linear correlation and regression or non-parametric regression analyses were used to test for relationship between height and serum glucose level during OGTT.

Results

Of all 1830 women with abnormal result of the challenge test, GDM was diagnosed in 293 women (16%) solely by a positive challenge test. In the remaining group of women (84%), a 75-g OGTT was performed. The WHO criteria diagnosed GDM in 1121 (61%) women, whereas 416 (23%) pregnant women had a normal diagnostic OGTT (false positive group). Among women with GDM (according to the WHO diagnostic criteria), 429 women (23%) also fulfilled the ADA diagnostic criteria for GDM. Overall, of all women with abnormal results of the challenge test, we identified 1414 women (77%) with GDM. The screening algorithm is depicted in Fig. 1.
Baseline clinical and anthropometric characteristics are given in Table 1. In comparison with the controls, women with GDM were significantly older and shorter, and had higher pregravid weight, BMI, and glucose level both at the first obstetric visit and during the challenge test. While comparable differences were found between the control group and the false positive group, both of these groups had a similar average height. Women with GDM frequently had a personal history of macrosomia and prior GDM and a family history of type 2 diabetes.

Through additional application of the ADA criteria, two groups of women with GDM were identified: those who fulfilled both diagnostic criteria (WHO(+)ADA(+)) and women who fulfilled the WHO criteria but not the ADA criteria (WHO(+)ADA(-)). Thus, we analyzed groups with an increasing severity of GDM: the controls!false positive!WHO(+)ADA(-)WHO(+)ADA(+)challenge test positive. Table 2 summarizes the parameters of glucose tolerance in these groups of women. As expected, most severe abnormalities of glucose metabolism were found in women with a positive challenge test and in the WHO(+)ADA(+) group. In both groups, a similar percentage of women required insulin therapy, whereas the requirement of insulin therapy was rare for WHO(+)ADA(-) women.

As shown in Fig. 2, pregravid BMI and height are associated with the severity of glucose intolerance during pregnancy. Regardless of the criteria used for diagnosis, women with GDM and a family history of type 2 diabetes

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Baseline characteristics of the women with gestational diabetes mellitus, those with a false positive challenge test, and the controls.</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>(n=1011)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>27.5 ± 4.7</td>
</tr>
<tr>
<td>Pregravid body mass index (kg/m²)</td>
<td>21.9 ± 3.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.7 ± 5.6</td>
</tr>
<tr>
<td>Weight before pregnancy (kg)</td>
<td>60.3 ± 10.6</td>
</tr>
<tr>
<td>Prior gestational diabetes (n)</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>Multiparity (n)</td>
<td>425 (42.0%)</td>
</tr>
<tr>
<td>Prior macrosomia (n)</td>
<td>32 (3.2%)</td>
</tr>
<tr>
<td>Family history of type 2 diabetes (n)</td>
<td>52 (5.1%)</td>
</tr>
</tbody>
</table>

Data are means ± s.d. *P<0.001 compared to the controls; †P<0.001 compared to the false positive group; ‡P<0.0001 (χ² test).
than the healthy controls. However, despite differences in the severity of glucose intolerance, height did not differ significantly between the GDM groups. The differences in height were not significant between GDM women who required insulin therapy and those treated with diet alone (163.3 ± 7.6 and 164.1 ± 6.1 cm respectively; \( P = 0.12 \)). However, there was a relationship between pregravid BMI and the severity of glucose intolerance. Furthermore, women treated with insulin had a higher BMI than women treated with diet only (26.02 ± 5.7 vs 23.4 ± 4.8; \( P < 0.001 \)).

In the univariate logistic regression analysis, height was a strong predictor for GDM, and an increase in height by 1 cm was associated with a 4.8% decreased risk for GDM (OR 0.952, 95% CI: 0.94–0.96; \( P < 0.00001 \)). Multivariate logistic regression analysis was performed to identify significant and independent factors that increase risk for GDM. The variables included in the analysis were age, weight before pregnancy, height, weight gain during pregnancy, prior GDM, prior macrosomia, and family history of type 2 diabetes (Table 3). All the studied variables, including height, were independently associated with GDM. Even after adjustment for confounding variables, height was still associated with GDM (OR 0.958, 95% CI: 0.94–0.97; \( P < 0.00001 \)). Therefore, we calculated the ROC in order to define a cut-off value for height, below which the risk of GDM substantially increases. The calculated cut-off value was 163 cm. However, the area under the curve was 0.4188 ± 0.0107, which did not allow for assumption of this value as predictive for GDM due to a poor discriminatory power. Moreover, cut-off sensitivity and specificity were also low (42.7 and 46.6% respectively). In all women who underwent a 75-g OGTT, there was a weak but significant inverse correlation between height and 2-h glucose level (\( R = -0.13; P < 0.00001 \)), but not with the fasting glucose level (\( R = -0.04; P = 0.12 \)). Similarly, a significant inverse association of height adjusted for age and pregravid weight with 2-h glucose level was found (\( \beta = -0.12; P < 0.00001 \)).

**Discussion**

This retrospective study in a Polish Caucasian population demonstrates that height is associated with a risk of GDM, and that women with GDM are shorter than healthy pregnant women. Our results also indicate that the height of women with GDM was similar despite different severities of glucose tolerance and different treatment regimens. These findings are partially consistent with earlier studies demonstrating significant differences in the height of women with and without GDM (6–12). Although this phenomenon has not yet been fully explained, there is possibly a direct link between the components of height and abnormal glucose tolerance. Asao et al. (4) have demonstrated that in the general US population, short legs and a low leg length to height ratio are commonly associated with obesity, insulin resistance, and type 2 diabetes. The British Women’s Heart and Health Study (5) also
demonstrated that decreased leg length or leg to trunk length ratio was associated with type 2 diabetes and insulin resistance in older women. Short legs and a low leg to trunk ratio in adults may reflect abnormal growth during childhood, and adult leg length can be used as an indicator of infant nutrition (18, 19). Individuals who were breastfed in infancy and were well fed in the first 4 years of childhood were shown to have longer legs in adulthood (19, 20) and a lower risk for type 2 diabetes (20, 21). Earlier attempts to understand the relationship between short stature and glucose intolerance have considered at least three essential factors: genetic predisposition, influence of the intra-uterine environment on fetal metabolic programming (which in turn affects both height and diabetes risk (21, 22)), and poor socioeconomic circumstances during childhood (6, 7, 9). On the other hand, recent studies have suggested an interesting hypothesis that the variations in height might influence the OGTT results. It was demonstrated that among subjects who underwent a 75-g OGTT, women had higher 2-h plasma glucose levels than men. However, this gender difference disappeared after adjusting for height (23–25). This relationship between height and 2-h glucose levels might be explained by the different metabolism of a standard dose of glucose during OGTT in shorter and taller subjects. Subjects with a short stature may have impaired metabolism of 75 g glucose in comparison with taller individuals because of a lower mass of metabolically active tissues, predominantly fat-free mass (24). Therefore, the incidence of diabetes mellitus and impaired glucose tolerance in individuals with a short stature may be overestimated. This is in line with our findings because in our cohort short stature was significantly associated with a higher 2-h glucose value. To elucidate this phenomenon, further studies on the metabolic and anthropometric determinants of glucose metabolism are necessary.

In our study, we used the different diagnostic criteria and different treatment regimens to stratify women with GDM into subgroups that reflected the severity of glucose intolerance. Interestingly, while women with GDM were significantly shorter than the controls or women with a false positive challenge test, increased GDM severity was not associated with a decrease in height. Similarly, women treated with diet alone had an average height that was comparable to that of the women who required additional treatment with insulin. This is the first study to evaluate the association between short stature and severity of GDM in Caucasian women. In a sample of Greek pregnant women with various forms of abnormal glucose tolerance (pregravid type 1 and type 2 diabetes, GDM, or one abnormal glucose value in a 100-g OGTT), Anastasiou et al. (6) found that there was a gradual decrease in mean height with worsening glucose intolerance. A similar trend, but not associated with different diagnostic criteria for GDM, was observed in Korean (7) and Brazilian (9) women with GDM. Interestingly, our study found that while the height of women with any degree of glucose intolerance did differ significantly, women with more severe glucose intolerance were significantly heavier before pregnancy, leading to a higher pregravid BMI. Body mass-related insulin resistance was associated with both more severe hyperglycemia and an insulin therapy requirement. We also found that women with a false positive challenge test had an average height that was similar to that of the healthy controls, which is inconsistent with previous studies reporting a decreased average height in women with a false positive screening test (1-h plasma glucose ≥7.2 mmol/l) (7) or one abnormal value in a 100-g OGTT (6). These discrepancies seem to reflect anthropometric variations among ethnic groups, as Polish Caucasian women are taller than Korean or Mediterranean women. Moreover, application of different diagnostic criteria for GDM would also affect the results, as using the National Diabetes Data Group GDM criteria may lead to the underdiagnosis of the condition by excluding women with relatively mild glucose intolerance, especially in groups with a false positive screening test. The problem of different diagnostic criteria for GDM also applies to our study. If we used only the ADA criteria, women classified as WHO(+)/ADA(−) would have been considered false positives instead of being treated. However, these women had different anthropometric characteristics and glucose metabolism parameters than the false positive group under the WHO criteria, and as much as 20% of the WHO(+)/ADA(−) women required insulin therapy.

Univariate and multivariate logistic regression analyses showed that height was an independent predictor of abnormal glucose tolerance during pregnancy, consistent with previous research (7, 10). However, the clinical relevance of this is unclear. The calculated cut-off value for height in our sample (163 cm) had low specificity and sensitivity, meaning its discriminating value seems to be relatively weak. BMI better identified subjects at risk for GDM and type 2 diabetes than short stature (22, 26). The mean height differs significantly among different ethnic and socioeconomic groups. Therefore, short stature will not likely be considered a risk factor when screening for GDM.

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>1.087</td>
<td>1.07–1.11</td>
</tr>
<tr>
<td>Weight before pregnancy</td>
<td>1.071</td>
<td>1.05–1.09</td>
</tr>
<tr>
<td>Height</td>
<td>0.957</td>
<td>0.94–0.98</td>
</tr>
<tr>
<td>Weight gain during pregnancy</td>
<td>1.045</td>
<td>1.03–1.07</td>
</tr>
<tr>
<td>Previous gestational diabetes</td>
<td>5.101</td>
<td>2.67–9.76</td>
</tr>
<tr>
<td>Previous macrosomia</td>
<td>1.515</td>
<td>1.03–2.23</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>2.866</td>
<td>2.28–3.59</td>
</tr>
</tbody>
</table>
By using a two-step diagnostic algorithm, we identified a false positive group of women. On the basis of current knowledge, these women might be considered as normal glucose-tolerant subjects. However, in the present study, in comparison with the controls, women with a false positive challenge test were significantly heavier, had higher (although still within the normal range) fasting glucose level, and more frequently had a family history of type 2 diabetes and prior GDM. There is no widely accepted method to manage such cases during pregnancy. While many obstetric providers treat false positive women with more intensive observation or therapy, identifying these patients as ‘glucose intolerant’ or ‘borderline diabetes’, others maintain that such patients do not warrant additional therapies (27). However, there is an increasing body of evidence that women with a false positive test are at risk not only for developing diabetes in the future but also for adverse perinatal outcome, including overall perinatal adversity, developing diabetes in the future but also for adverse pregnancy outcomes. Women with a false positive test are at risk not only for developing diabetes in the future but also for adverse perinatal outcome, including overall perinatal adversity, endometritis, shoulder dystocia, fetal macrosomia, and antenatal death (27, 28). Before changes in clinical practice can be recommended, further studies including cost–benefit analysis of providing additional therapy to these pregnant women are needed.

There are some obvious limitations of our retrospective study. First, we had no patient data from childhood, such as birth weight and length, and were thus unable to determine the independent contributors of pre- versus postnatal factors in glucose tolerance in adulthood. Secondly, we did not identify a group of women diagnosed with GDM using only the ADA criteria. Given that as few as 18% of pregnant women with GDM (as diagnosed by both the ADA and WHO criteria or the WHO criteria only) fulfill the ADA criteria (17), analyzing a group that used only this diagnostic criteria seems relevant.

In conclusion, Caucasian women with GDM are shorter than pregnant women without GDM regardless of the diagnostic criteria used or the severity of glucose intolerance. Although height is an independent predictor for GDM, its predictive value for identifying women at risk is relatively low, and should not be considered in selective screening for this disease.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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