Impact of maternal height and gestational diabetes mellitus on offspring birthweight

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ABSTRACT

Aims: To evaluate the impact of gestational diabetes mellitus (GDM) and maternal height on offspring birthweight.

Methods: This is an observational cohort study, encompassing 4 111 Finnish primiparous women from Vantaa city, Finland, with singleton deliveries between 2009 and 2015. Data were obtained from the Finnish Medical Birth Register. The study population was divided into five groups according to maternal height. Cut-offs for height levels were I \( \leq 158 \) cm, II 159–163 cm, III 164–167 cm, IV 168–172 cm, V \( \geq 173 \) cm. The main outcome measure was offspring birthweight, expressed as Z-scores according to sex and gestational age.

Results: Independently, both maternal height and GDM increased offspring birthweight (\( p < 0.001 \) for height and GDM). When studying the interaction, a significant increase in offspring birthweight was noted only in extreme height categories; group I \( \leq 158 \) cm (\( p = 0.011 \)), group IV 168–172 cm (\( p = 0.010 \)) and group V \( \geq 173 \) cm (\( p < 0.001 \)) and the impact was similar in both sexes. Maternal height had no impact on offspring ponderal index (\( p = 0.20 \) for trend).

Conclusions: In extreme height categories, short and tall primiparous women with GDM are at risk for delivering larger offspring compared to women without GDM of similar height.

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This study has been conducted in the city of Vantaa, Finland and in the city of Helsinki, Finland.

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1. Introduction

Fetal growth is a complex and multifactorial process influenced by several factors including genetic factors, in utero environment, maternal metabolism, duration of pregnancy and neonatal sex [1,2]. Of pregnancy complications, hypertensive disorders and gestational diabetes mellitus (GDM) are the best known underlying factors affecting fetal growth [3–5]. Offspring birth size, especially when considered macrosomic, increases the risk for delivery complications such as prolonged labor, operative vaginal delivery, cesarean section and admission of the newborn to neonatal centers [6]. Furthermore, a non-optimal fetal growth environment has been shown to have long-term effects on cardiovascular and metabolic disturbances, partly through its impact on birth size [7]. Due to short- and long-term health consequences associated with body size at birth, it is of interest to study factors potentially influencing fetal growth.

GDM is a common pregnancy complication and has long been defined as any kind of abnormal glucose metabolism with onset or first detection during pregnancy [8]. Recent definitions are more precise in differentiating between pre-existing diabetes mellitus and GDM, depending on either different diagnostic criteria using 2-h 75-g oral glucose tolerance test (OGTT) or timing of diagnosis during pregnancy [9–11]. The prevalence of GDM varies between 2% and 32% with a 9% median estimate for North America and 6% for Europe [12]. GDM is known to increase the risk of macrosomia and metabolic disturbances for both mother and child later in life [13–16].

Maternal anthropometry and its effects on fetal growth have been widely studied. Pre-pregnancy body mass index (BMI) has a direct effect on offspring birthweight and obesity increases the risk of macrosomia [17]. It has also been shown that GDM augments the effects of maternal BMI on offspring birthweight when combined [5,18,19]. Maternal stature has been shown to be positively associated with newborn size at birth [20–22]. Glucose metabolism itself is also affected by anthropometry. In non-pregnant, non-diabetic individuals it has been shown that taller people with a BMI below 35 kg/m² tend to have lower postprandial glucose levels compared to shorter people with the same BMI, using standard 2-h 75-g OGTT, with no difference in fasting glucose levels [23]. It has also been shown that short stature in pregnant women is associated with elevated postprandial glucose levels with no difference in fasting glucose levels [24,25].

In 2016, we initiated a long-term follow-up cohort study in the city of Vantaa, Finland, to assess both short- and long-term consequences of disturbances in glucose regulation on women’s and their offspring’s health. Since it has been shown that stature in pregnant women affects offspring size at birth and alters glucose metabolism, the aim of this study is to simultaneously study the impact of maternal height and GDM on offspring birthweight.

2. Materials and methods

2.1. Subjects

This study is an observational cohort study in the city of Vantaa, the fourth biggest city in Finland. Between January 1st 2009 and December 31st 2015, 7 750 primiparous women without a history of previously diagnosed diabetes mellitus gave birth. Of those, 4 111 women with Finnish background (born in Finland with Finnish or Swedish as mother tongue) and aged ≥18 years gave birth to a singleton offspring between gestational weeks 37 and 42 and had complete height and weight data together with complete data from a standard 2-h 75-g OGTT. The Finnish Current Care Guidelines for GDM recommends screening of all pregnant women during their first pregnancy for GDM using 2-h 75-g OGTT, except in low-risk patients, i.e. women aged under 25 years, with a BMI between 18.5– and 25 kg/m² and with no family history of diabetes [26].

Data on maternal-fetal characteristics and pregnancy outcomes were obtained from the Medical Birth Register, which is administrated by the National Institute for Health and Welfare in Finland and receives the information from all Finnish maternity hospitals. The following information on the primiparous women was obtained from this source: pre-gestational weight, height, previous pregnancies (miscarriages, induced abortions or ectopic pregnancies) and deliveries, infertility treatment, smoking during pregnancy, and hospitalization due to hypertension during pregnancy [27]. The following information on the offspring was collected: sex, birth length, birthweight, and head circumference.

GDM was defined according to the Finnish Current Care Guidelines for GDM as one or more pathological glucose values in a standard 2-h 75-g OGTT [26]. The diagnostic thresholds were: fasting plasma glucose ≥ 5.3 mmol/L, 1-h glucose ≥ 10.0 mmol/L, and 2-h glucose ≥ 8.6 mmol/L [26]. Macrosomia was defined as offspring birthweight > 4500 g. Large for gestational age (LGA) and small for gestational age (SGA) were defined as a birthweight >90th percentile and <10th percentile, respectively, according to gestational age and sex. Ponderal index (PI), was calculated for estimating body proportionality at birth and was defined as birth weight (kg) divided by birth length (m) in third power: PI = kg/m³ [28].

Educational attainment was defined according to years of schooling, as obtained from Statistics Finland [29].

2.2. Statistical analysis

Data are presented as means with range or standard deviations (SD) or as counts with percentages. Standardized values were divided into five height level categories using z-scores: I (−1.5), II (−1.5 to <−0.319), III (−0.319 to <0.319), IV (0.319 to <1.15), and V (≥1.15) corresponding to grades containing 12.5, 25, 25, 25, and 12.5% of the total distribution. Cut-offs for maternal height levels were I ≤ 158 cm, II 159–163 cm, III
Offspring birthweight and PI were calculated as Z-scores (according to sex and gestational age). Statistical significances for the unadjusted hypothesis of linearity across categories of height levels were evaluated by using the Cochran-Armitage test for trend and analysis of variance with an appropriate contrast. Adjusted hypothesis of linearity (orthogonal polynomial) was evaluated using generalized linear models (e.g. analysis of covariance and logistic models) with appropriate distribution and link function. Models included age, education years and prepregnancy body mass as covariates. A possible nonlinear relationship between prevalence of GDM or offspring birthweight and the maternal standardized height was assessed by using 5-knot-restricted cubic spline regression. The length of the distribution of knots was located at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles corresponding to standardized height values of −1.66, −0.66, 0.01, 0.67 and 1.67. For restricted cubic splines, also known as natural splines, knot locations are based on Harrell’s recommended percentiles or user-specified points [30]. The normality of the variables was tested by using the Shapiro–Wilk W test. Statistical significance was set at p < 0.05. Stata 15.0 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

2.3 Ethical approval

This study has been approved by the ethics committee of the Hospital District of Helsinki and Uusimaa (356/13/03/03/2015, November 2nd 2015), and by the health authority of Vantaa city, Finland. Permission to use register data for this study were given by the National Institute for Health and Welfare, and Statistics Finland. According to the ethics committee of Hospital District of Helsinki and Uusimaa, and the health authority of Vantaa city, the study participants do not need to provide the Statement of Informed Consent, since this is an observational register-based study and the registered people were not contacted.

3. Results

3.1 Characteristics of the study participants

Baseline characteristics of the 4 111 study participants divided into five height levels are shown in Table 1. The cutoffs were: I ≤ 158 cm, II 159–163 cm, III 164–167 cm, IV 168–172 cm, and V ≥ 173 cm. Mean height of the study participants was 166.0 (SD 6.0) cm. Height was positively associated with age and educational attainment (both p < 0.001).

Baseline characteristics of the offspring according to maternal height levels are shown in Table 2. Boys had a mean birthweight of 3 564 (SD 466) g, birth length 50.7 (SD 2.0) cm, and head circumference 35.3 (SD 1.4) cm, while the corresponding values for girls were 3 458 (SD 446) g, 49.9 (SD 2.0) cm, and 34.8 (SD 1.4) cm, respectively. Maternal height was positively associated with offspring birthweight, birth length, and head circumference in both sexes, as well as with a higher prevalence of macrosomia and large for gestational age (LGA) newborns (all p < 0.001). In contrast, maternal height was inversely associated with small for gestational age (SFGA) newborns (p < 0.001).
Table 2 – Baseline characteristics of the 4 111 offspring according to maternal height.

<table>
<thead>
<tr>
<th>Characteristics of the offspring</th>
<th>Height levels</th>
<th>p-value for linearity</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 442</td>
<td>N = 990</td>
<td>N = 974</td>
</tr>
<tr>
<td><strong>Boys, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>238 (54)</td>
<td>516 (52)</td>
<td>527 (54)</td>
</tr>
<tr>
<td><strong>Birthweight (g), mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>3 435 (451)</td>
<td>3 483 (443)</td>
</tr>
<tr>
<td>Girls</td>
<td>3 304 (441)</td>
<td>3 406 (415)</td>
</tr>
<tr>
<td><strong>Birth length (cm), mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>50.0 (2.0)</td>
<td>50.3 (1.9)</td>
</tr>
<tr>
<td>Girls</td>
<td>49.1 (2.0)</td>
<td>49.7 (1.9)</td>
</tr>
<tr>
<td><strong>Birth weight (Z-score), mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>−0.31 (0.94)</td>
<td>−0.18 (0.95)</td>
</tr>
<tr>
<td>Girls</td>
<td>−0.37 (0.94)</td>
<td>−0.17 (0.91)</td>
</tr>
<tr>
<td><strong>Ponderal index, (weight [kg]/ height [m]²), mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>27.4 (2.6)</td>
<td>27.2 (2.4)</td>
</tr>
<tr>
<td>Girls</td>
<td>27.4 (2.6)</td>
<td>27.8 (2.3)</td>
</tr>
<tr>
<td><strong>Head circumference (cm), mean (SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>35.0 (1.5)</td>
<td>35.1 (1.4)</td>
</tr>
<tr>
<td>Girls</td>
<td>34.3 (1.5)</td>
<td>34.7 (1.3)</td>
</tr>
<tr>
<td><strong>Macrosomia (birthweight ≥ 4500 g), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>2 (0.5)</td>
<td>12 (1.2)</td>
</tr>
<tr>
<td>Girls</td>
<td>22 (5.0)</td>
<td>66 (6.7)</td>
</tr>
<tr>
<td><strong>LGA (&gt;90 h percentile), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boys</td>
<td>69 (15.6)</td>
<td>122 (12.3)</td>
</tr>
</tbody>
</table>

SD, standard deviation.
Statistical significances for the unadjusted hypothesis of linearity across categories of height levels were evaluated using Cochran-Armitage test for trend and analysis of variance.

*Cut-offs for the different height levels were I ≤ 158 cm, II 159–163 cm, III 164–167 cm, IV 168–172 cm, and V ≥ 173 cm.
age (SGA) newborns (p < 0.001). Ponderal index of newborns did not differ across different maternal height levels.

3.2. Maternal height and prevalence of gestational diabetes

Fig. 1 shows the prevalence of GDM at five different height levels and on a continuous scale with standardized height, adjusted for age and educational attainment. The prevalence of GDM was highest among the shortest women (<158 cm) with a prevalence of 23.9% (95% CI 19.9–27.9) and lowest in the group of average height women (164–167 cm) with a prevalence of 18.7% (95% CI 15.5–21.9) (Fig. 1B). There was an inverse relationship across maternal height levels and prevalence of GDM (p = 0.018 for linearity).

3.3. Effect of maternal height and gestational diabetes on offspring birthweight and ponderal index

Fig. 2 shows the impact of maternal height and GDM and their interaction on offspring birthweight, adjusted for maternal age, pre-pregnancy BMI and educational attainment. In primiparous women without GDM, offspring birthweight increased with maternal height (p < 0.001 for trend). Similarly, in primiparous women with GDM offspring birthweight increased with maternal height (p < 0.001 for trend), except in women of average height (159–167 cm) which included about half of the study participants, in whom GDM had no significant influence on offspring birthweight. Maternal height had no impact on offspring PI (p = 0.20 for trend, adjusted for maternal age, pre-pregnancy BMI and educational attainment) (Fig. 3). The impact of maternal height and GDM on offspring birthweight was similar for both sexes, as shown in Fig. 4.

4. Discussion

According to the study findings in our cohort including Finnish women and their offspring, in primiparous women without GDM, offspring birthweight increased with maternal height (p < 0.001 for trend). Similarly, in primiparous women with GDM offspring birthweight increased with maternal height (p < 0.001 for trend), except in women of average height (159–167 cm) which included about half of the study participants, in whom GDM had no significant influence on offspring birthweight. Maternal height had no impact on offspring PI (p = 0.20 for trend, adjusted for maternal age, pre-pregnancy BMI and educational attainment) (Fig. 3). The impact of maternal height and GDM on offspring birthweight was similar for both sexes, as shown in Fig. 4.
across different maternal height levels. Moreover, maternal height and GDM had no impact on PI.

The nationwide prevalence of GDM in Finland increased during our study period from 11.2% to 15.9% in 2015 [27]. The high prevalence of GDM in our cohort is in line with nationwide findings. Overall, GDM prevalence can be considered high in Finland, when compared to a median estimate of 6% in Europe, even though GDM prevalence have been shown to vary between 2 and 32% globally [12]. The comprehensive screening for GDM since 2008 in Finland might possibly explain this rather high prevalence in our country and particularly in this study, in which only women with high-risk for GDM with complete OGTT data were included.

Our findings regarding maternal height and offspring birthweight in pregnancies without GDM were expected. Many other studies have shown a positive association between maternal height and offspring birth size [20–22,31]. Moreover, the positive association between maternal height and LGA babies, as well as the negative association between maternal height and SGA babies have been recognized previously. In fact, a recent German study reported similar relationships [32]. Interestingly, neither maternal height nor GDM had any impact on PI. This might indicate that body proportions did not differ across different maternal height levels at term.

The association between maternal height and offspring birth size has been thought to reflect mainly genetic factors [21], although the height of the mother and offspring body size, especially in developing countries, are also consequences of the nutritional status early in life [33]. Further, some physical aspects are thought to explain the correlation, including maternal constraint. In shorter mothers, there can be physical limitations for the growth of the uterus that can restrict fetal growth [34].

In most previous studies, a positive correlation between GDM and offspring birth size has been reported, but the effect of GDM on offspring birth size has been studied with no distinction of maternal stature [4,13,35]. In 1952, Jørgen Pedersen theorized that hyperglycemia of the mother led to hyperglycemia of the fetus and that this, in turn, amplified the fetal response to insulin [36]. Pedersen’s hypothesis has formed the basic understanding of the pathophysiological consequences of diabetes during pregnancy. Modifying Pedersen’s hypothesis has led to the idea, that the impact of GDM on birth size is thought to be due to insulin resistance in diabetic mothers and an elevated glucose level that passes through the placenta. This, in turn, increases the insulin levels of the fetus and leads to an excessive uptake of glucose, storage of glycogen and the formation of adipose tissue, resulting in macrosomia [13]. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study showed no threshold for glucose in relation to adverse pregnancy outcomes [4]. The results indicated a strong, positive and continuous association between increasing maternal glucose concentrations, already below those that are diagnostic for diabetes mellitus, and an increased birthweight [4].

GDM is a heterogenic metabolic disorder and is thought to be caused by increasing insulin resistance due to placental hormonal influence and maternal adiposity in late pregnancy, impaired beta-cell function, genetic predisposition and in some cases autoimmunity [37]. Glucose metabolism has been shown to be affected by stature both in non-pregnant and pregnant individuals. In non-pregnant individuals, studies have shown that taller individuals tend to have lower postprandial glucose levels compared to shorter individuals using standard OGTT, with no difference in fasting glucose levels [23–25,38–40]. In line with our findings, previous studies have also proven GDM to be more common in shorter women [24,25,41], although some findings show no differences in stature between GDM and non-GDM women [42].

It is not fully understood how stature influences glucose metabolism, but there are several hypotheses trying to explain the association. Taller people have more muscle mass, although not necessarily a higher percentage of muscle tissue in relation to total body mass. It is generally accepted that muscle tissue is the major tissue involved in glucose metabolism [39]. It has been theorized that the inverse association between height and postprandial glucose levels after a standard 2-h OGTT reflects the larger amount of metabolically active muscle tissue that taller individuals, compared to shorter individuals, have to metabolize the same fixed load of glucose [39]. Height has also been positively associated with both pancreatic beta cell function and insulin sensitivity [38], possibly indicating a more favorable glucose regulation in tall, compared to short individuals.

According to our findings, the simultaneous effect of maternal height and GDM affects offspring birthweight only in the extreme height categories of short and tall women. In Finland, GDM is diagnosed using a fixed load of 75-g glucose in association with a 2-h OGTT, regardless of maternal height, weight or body composition. The varying effect of GDM on offspring birthweight observed in different maternal height levels can probably partly be explained by differences in maternal anthropometrics including body composition. Perhaps, taller women with GDM might have a more severe degree of impairment in their glucose regulation compared to shorter women, consequently more often leading to macrosomia among the offspring. Among short women, it is possible that the muscle mass is limited – both quantitatively and qualitatively – and thus already a mild elevation in glucose concentration is more likely to affect the fetus.

One can also speculate about possible effects of assortative mating on stature and paternal genetic imprinting on traits and disease burden in the fetus. According to a meta-analysis about assortative mating for human heights there is a moderate positive trend for assortative mating for height despite ethnicities, although, height cannot be considered as a major factor when choosing a partner [43]. Similarly, it is important to knowledge the possible impact of a short mothers’ own early growth and nutritional status. Birth size is known to be positively associated with adult height [44], in other words might short individuals have had a low birthweight and a non-optimal prenatal growth. There are several studies indicating that intrauterine growth restriction and malnutrition in infancy can lead to impaired glucose regulation and impaired endogenous pancreatic function in adulthood, predisposing to type 2 diabetes [45,46].

The question remains why offspring birthweight is not affected by GDM in women of average height? Interestingly, a recent Australian study shows no elevation at macrosomia
rates in diet-treated GDM women compared to non-diabetic controls, suggesting that a milder and diet-treated GDM could have a lower impact on risk of macrosomia [47]. Possibly, GDM is milder in women of average height where the influence of stature on glucose metabolism would be less.

To the best of our knowledge, this is the first study to investigate the simultaneous effect of maternal height and GDM on offspring birthweight. According to our study findings, GDM increased offspring birthweight only in women with short or tall stature, while among the majority of women of average height no impact of GDM on birth size was observed. In clinical practice, this might indicate that both short and tall primiparous women with GDM should have a more intense follow up during pregnancy, and if needed, a customized plan for delivery. This area needs to be further explored, also taking into account the mother’s own birthweight and potential transgenerational aspects.

The strength of this study is that the study cohort encompasses all adult Finnish primiparous women from the city of Vantaa, the fourth largest city in Finland, who gave birth to a singleton infant at term during a seven-year follow-up. The diagnosis of GDM is based on a 2-h 75-g oral glucose tolerance test and is considered reliable while it is standardized nationwide, and the diagnostic criteria have been the same during the follow-up period.

The study has some limitations. We had no information on measures of insulin resistance, gestational weight gain, family history of diabetes, physical activity nor dietary habits. We also missed data on paternal anthropometry. Body composition and birthweight of the mothers’ were unknown. In this cohort all study participants were Finnish, therefore the generalization of our results globally can be limited. Noteworthy is that even if all women included in the study had a reliable GDM diagnosis based upon OGTT results, we have no other information on metabolic parameters and associations between these and offspring birthweight were unknown.

In conclusion, short and tall Finnish primiparous women with GDM are at risk of delivering larger infants compared to women without GDM with the same height. GDM does not affect offspring birthweight in Finnish primiparous women of average height. Among tall Finnish women with GDM, the prevalence of macrosomia is increased. Maternal height had no impact on offspring PI. To minimize the adverse effects of an increased birthweight and/or macrosomia, special attention should be paid to women with GDM, especially in the subgroups of short and tall women.

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Conflict of interest
None.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.01.004.

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