Prepregnancy Body Mass Index and Offspring Birth Weight in Women with Type 1 and Type 2 Diabetes

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Abstract

**Objective:** To evaluate offspring birth weight in relation to prepregnancy body mass index in women with pregestational diabetes.

**Methods:** A cohort study of 260 consecutive women with type 1 or type 2 diabetes, included January 2012 to May 2014, and classified as normal weight (prepregnancy body mass index < 24.9 kg/m²), overweight (25.0-29.9) or obese (≥30.0).

**Results:** Among 155 women with type 1 diabetes, 55% were normal weight, 27% overweight and 18% obese. Corresponding figures among 105 women with type 2 diabetes were 15%, 22% and 63%. HbA1c in early and late pregnancy and gestational weight gain were comparable across the body mass index categories in both diabetes types. Offspring birth weight across the body mass index categories was 3,514 ± 471 vs. 3,534 ± 483 vs. 3,483 ± 499 g (mean ± SD) (P=0.85) for type 1 diabetes and 3,113 ± 767 vs. 3,221 ± 567 vs. 3,296 ± 839 g (P = 0.39) for type 2 diabetes. There were no associations between prepregnancy body mass index and offspring birth weight or birth weight SD-score after adjustment for HbA1c, excessive gestational weight gain, parity, ethnicity, smoking and diabetes type. Women with type 1 diabetes had higher gestational weight gain (15.1 ± 6 vs. 11.9 ± 7 kg, P < 0.001), offspring birth weight (3,514 ± 476 vs. 3,251 ± 772 g, P < 0.001) and birth weight SD-score (1.04 ± 1.3 vs. 0.43 ± 1.7, P < 0.001) compared to type 2 diabetes while HbA1c was comparable.

**Conclusion:** In women with pregestational diabetes, offspring birth weight was not associated with prepregnancy body mass index. Gestational weight gain and offspring birth weight were higher in women with type 1 compared to type 2 diabetes.

Introduction

Large for gestational age infants still occur in up to half of the pregnancies in women with type 1 or type 2 diabetes [1] which is a clinical challenge both during delivery and later in life [2,3]. In the short term, these infants run a higher risk of neonatal complications like preterm delivery, delivery by cesarean section, shoulder dystocia and fetal asphyxia [4, 5]. Individuals who are born large for gestational age are likely to develop diabetes, obesity or cardiovascular diseases later in life compared to individuals with appropriate birth weight [6].

Both maternal diabetes and obesity in otherwise healthy women, are associated with increased risk of large for gestational age infants [7-11]. For women with diabetes, it is well-known that maternal hyperglycemia, especially late in pregnancy, results in accelerated fetal growth, and that aiming for normoglycemia is crucial in order to reduce the prevalence of large for gestational age infants [3,8,12-14]. Excessive maternal gestational weight gain is yet another factor associated with fetal overgrowth and adverse pregnancy outcomes in women with type 1 and 2 diabetes [15-18]. Higher maternal prepregnancy BMI may also be associated with poor pregnancy outcome in women with type 1 diabetes [7, 14], while data on women with type 2 diabetes are limited [14]. In addition the impact of HbA1c and/or gestational weight gain was not taken into account in these studies [7, 14]. Evidence on the impact of prepregnancy BMI on pregnancy outcomes in women with diabetes, regardless of glycemic control and gestational weight gain, is therefore so far very sparse. In this study we aim to evaluate the association between maternal prepregnancy BMI and offspring birth weight, in an unselected cohort of women with type 1 and type 2 diabetes.

Research Design and Methods

This cohort study includes all consecutive, singleton pregnancies in women with type 1 and type 2 diabetes giving birth after 22 weeks from January 2012 to May 2014 at the Center for Pregnant Women with Diabetes, Rigshospitalet, Denmark. The women originate from a geographic well-defined region of 2.4 million inhabitants. Most of the included women (86%) attended their first visit before 14 gestational
weeks. The majority was diagnosed with either type 1 or type 2 diabetes prior to pregnancy however, 10 women were referred under the diagnosis gestational diabetes and were then reclassified as newly onset type 2 diabetes due to HbA1c > 6.5% (48 mmol/mol) in early pregnancy. Two women with previous bariatric surgery, two with severe concomitant illness, that could possibly bias the study aims, and two without information on prepregnancy BMI, were excluded. In total, 155 women with type 1 diabetes and 105 women with type 2 diabetes were included.

Maternal and infant data were obtained from medical records and registered prospectively in a local quality assessment database, Clinical Measure System (Klinisk Måle System), by our staff immediately after the first visit in pregnancy and after delivery. Approval from the Danish Data Protection Agency was obtained. Due to the retrospective design, approval from The Danish National Committee on Biochemical Research Ethics was not required.

**Prepregnancy BMI and gestational weight gain**

According to prepregnancy BMI based on self-reported pregestational weight and height [16, 18], the women were classified as underweight (<18.5 kg/m²), normal weight (18.5-24.9 kg/m²), overweight (25.0-29.9 kg/m²) or obese (≥30.0 kg/m²) [19]. Three underweight (BMI 17.0-18.3 kg/m²) women with type 1 diabetes, were included in the normal weight category due to their low number.

Total gestational weight gain was calculated as the difference between the weight measured at last visit before delivery and the self-reported prepregnancy weight [16, 18]. Within the three BMI categories, the total gestational weight gain was considered excessive (>16.0, >11.5, >9.0 kg) and insufficient (<11.5, <7.0, <5.0 kg) according to the Institute of Medicine (IOM) recommendations for normal weight, overweight and obese women respectively [20].

**Pregnancy care**

All women followed the routine pregnancy care program at our clinic with antenatal visits at 8, 12, 21, 27 and 33 gestational weeks [21]. At first pregnancy visit, all women had a one hour dietitian consultation for individual dietary planning following national guidelines for diabetes diet recommending a low glycemic index diet [16]. Women with BMI <30 kg/m² were recommended to gain 10-15 kg gestational weight gain in overweight women (25.0-29.9 kg/m²) was changed to 5-8 kg. Folic acid intake of at least 400 ug/day was tested for ketone bodies and protein [18].

Outcomes of the women with type 2 diabetes, oral hypoglycemic agents (mainly metformin), were discontinued at admission and further treatment was based on diet and insulin or diet alone [16]. In women with blood pressure ≥135/85 mmHg or urinary albumin excretion (UAE) > 300 g/24 hours, antihypertensive treatment was initiated and tailored with methyldopa as the primary agent [18].

**Data collection**

At first and last visit, the following clinical variables were registered in the local database according to local guidelines: Blood pressure, insulin type and daily insulin dose, antihypertensive agents, UAE and diabetic retinopathy. At first visit we also registered ethnicity, smoking habits and folic acid intake before and in early pregnancy. Perinatal outcome such as preterm delivery, offspring birth weight and gender and congenital malformations were also recorded.

**Outcome variables**

Proteinuria was defined as urinary albumin excretion ≥ 190 mg/24 h. Preterm delivery was defined as delivery before 37 completed gestational weeks. Offspring birth weight standard deviation score (SD-score) described how far, the birth weight was from the mean of the national standard population adjusted for gestational age and sex [22]. Large and small for gestational age infants were defined as offspring birth weight ≥90th or ≤10th centile adjusted for gender and gestational age. Induced abortions, based on sonographically verified malformations, were noted. Neonatal complications were defined as follows: neonatal jaundice (phototherapy required), transient tachypnea of the newborn (continuous positive airway pressure for >60 minutes), and neonatal hypoglycemia (plasma glucose < 2.5 mmol/l measured two hours after birth). Perinatal morbidity was defined as the incidence of at least one of the following complications: neonatal jaundice, transient tachypnea of the newborn, neonatal hypoglycemia or perinatal mortality [15].

**Statistical analysis**

Continuous variables are given as mean ± SD (standard deviation) and categorical variables as number (%). The three BMI categories were compared by trend test for continuous variables and Chi-square test for categorical variables. T-test was used for continuous variables when only two groups were compared. The correlation between the self-reported pre-pregnancy weight and the first measured weight in pregnancy was performed with univariate linear regression. To control for confounding when evaluating the impact of prepregnancy BMI (kg/m²) on offspring birth weight, we applied multiple linear regression with offspring birth weight (g) or offspring birth weight SD-score as dependent variables. Based on theoretical considerations, six possible confounders were included: excessive gestational weight gain according to the IOM guidelines (yes/no), HbA1c at last pregnancy visit (%), smoking (yes/no), diabetes type (type 1/type 2), nulliparity (yes/no) and Nordic Caucasian ethnicity (yes/no). The statistical analyses were made using IBM SPSS statistics 22 (SPSS, Chicago, IL, USA). A two-sided p-value <0.05 was considered to be statistically significant.

**Results**

Among 155 women with type 1 diabetes, 55% were normal weight, 27% overweight and 18% obese, while the figures for 105 women with type 2 diabetes were 15%, 22% and 63% (Table 1).
<table>
<thead>
<tr>
<th></th>
<th>All women</th>
<th>Normal weight</th>
<th>Overweight</th>
<th>Obese</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong></td>
<td>155</td>
<td>85 (55%)</td>
<td>42 (27%)</td>
<td>28 (18%)</td>
<td></td>
</tr>
<tr>
<td><strong>Type 2</strong></td>
<td>105</td>
<td>16 (15%)</td>
<td>23 (22%)</td>
<td>66 (63%)</td>
<td></td>
</tr>
</tbody>
</table>

**Duration of diabetes (years)**

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15.3±7.7</td>
<td>4.5±4.0**</td>
<td>4.6±4.4</td>
<td>5.7±6.1</td>
<td>4.0±3.3</td>
</tr>
</tbody>
</table>

**Prepregnancy BMI (kg/m2)**

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
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<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>25.7±4.9</td>
<td>31.8±6.5***</td>
<td>22.9±1.7</td>
<td>27.3±1.3</td>
<td>35.5±5.1</td>
</tr>
</tbody>
</table>

**Nordic Caucasian ethnicity**

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>144 (93%)</td>
<td>93 (51%)**</td>
<td>77 (91%)</td>
<td>39 (93%)</td>
<td>28 (100%)</td>
</tr>
<tr>
<td></td>
<td>53 (51%)</td>
<td>9 (56%)</td>
<td>9 (39%)</td>
<td>35 (53%)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**Smokers**

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>13 (8%)</td>
<td>7 (8%)</td>
<td>4 (9%)</td>
<td>2 (7%)</td>
<td>0.94</td>
</tr>
<tr>
<td></td>
<td>20 (19%)**</td>
<td>2 (12%)</td>
<td>3 (13%)</td>
<td>15 (23%)</td>
<td>0.46</td>
</tr>
</tbody>
</table>

**Nulliparous**

<table>
<thead>
<tr>
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<th>Type 2</th>
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<tbody>
<tr>
<td></td>
<td>87 (57%)</td>
<td>27 (26%)***</td>
<td>45 (54%)</td>
<td>27 (64%)</td>
<td>16 (24%)</td>
</tr>
<tr>
<td></td>
<td>58 (42%)</td>
<td>22 (55%)</td>
<td></td>
<td>10 (39%)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

**Diabetic retinopathy, at first visit**

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th></th>
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<tbody>
<tr>
<td></td>
<td>8 (9%)**</td>
<td>1 (7%)</td>
<td>3 (15%)</td>
<td>4 (7%)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

**Elevated urinary albumin excretion (> 30 mg/mmol)**

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th></th>
<th></th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>10 (7%)</td>
<td>5 (6%)</td>
<td>2 (5%)</td>
<td>3 (11%)</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>13 (13%)</td>
<td>5 (22%)</td>
<td></td>
<td>6 (10%)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

**Folic acid before pregnancy**

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>88 (49%)</td>
<td>36 (48%)</td>
<td>22 (55%)</td>
<td>10 (40%)</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>20 (23%)**</td>
<td>6 (43%)</td>
<td>6 (32%)</td>
<td>8 (15%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Table 1: Maternal baseline characteristics in 155 women with type 1 diabetes and 105 women with type 2 diabetes classified as normal weight, overweight or obese based on prepregnancy BMI. Numbers are given as mean ±SD or number (%). P-value denotes difference across the BMI categories. Chi-square test or unpaired t-test were used to compare type 1 diabetes with type 2 diabetes: *P < 0.05 **P < 0.01 ***P < 0.001. Normal weight (prepregnancy BMI <24.9 kg/m2), overweight (25.0-29.9) or obese (≥30.0).

HbA1c levels at first and last pregnancy visit were comparable across the three BMI categories and between women with type 1 and type 2 diabetes (Table 2). Offspring birth weight and birth weight SD-score were comparable across the BMI categories in both diabetes types (Table 3). In women with type 1 diabetes offspring birth weight was higher than in women with type 2 diabetes (mean 3,514 ± SD 476 vs. 3,251 ±772 g, P < 0.001) and the prevalence of small for gestational age infants was lower (4% vs. 13%, P = 0.008).
Table 2: Maternal clinical characteristics during pregnancy in 155 women with type 1 diabetes and 105 women with type 2 diabetes classified as normal weight, overweight or obese based on prepregnancy BMI (Numbers are given as mean ±SD or number (%). P-value denotes difference across the BMI categories. Chi-square test or unpaired t-test were used to compare type 1 diabetes with type 2 diabetes: *P <0.05 **P <0.01 ***P <0.001. Normal weight (prepregnancy BMI <24.9 kg/m2), overweight (25.0-29.9) or obese (≥30.0). Total gestational weight gain: Difference between the weight measured at last visit before delivery and the self-reported prepregnancy weight).

Total gestational weight gain decreased with higher prepregnancy BMI in both diabetes types (Table 2) and was higher in women with type 1 diabetes compared to women with type 2 diabetes (15.1 ± 6.1 vs. 11.9 ± 6.8 kg, P < 0.001), also within each BMI category (Table 2). The proportion of women with excessive gestational weight gain, according to the IOM guidelines, increased significantly with higher prepregnancy BMI in both diabetes types, and the majority of all women experienced excessive gestational weight gain (Table 2). A strong correlation between the self-reported pre-pregnancy weight and the weight at first pregnancy visit was seen (R2 = 0.96, p < 0.0001). Maternal weight was on average 2.3 kg higher in early pregnancy compared to the self-reported prepregnancy weight.

The prevalence of preterm delivery, caesarian section and neonatal jaundice was comparable across the three BMI categories for both diabetes types (Table 3).
Type 1 155 85 (55%) 42 (27%) 28 (18%) 2
Type 2 105 16 (15%) 23 (22%) 66 (63%) 0

Gestational age at delivery (days)
Type 1 264±8 263±9 265±6 265±7 0.39
Type 2 262±16 264±16 264±10 261±18 0.43

Preterm delivery
Type 1 23 (15%) 17 (20%) 4 (10%) 2 (7%) 0.13
Type 2 18 (17%) 2 (13%) 3 (13%) 13 (20%) 0.66

Offspring birth weight (g)
Type 1 3,514±476 3,514±471 3,534±483 3,483±499 0.85
Type 2 3,251±772*** 3,113±767 3,221±567 3,296±839 0.39

Offspring birth weight SD-score
Type 1 1.04±1.3 1.1±1.3 1.0±1.3 0±1.4 0.48
Type 2 0.43±1.7*** -0.09±1.5 0.25±1.2 0.63±1.8 0.1

Large for gestational age infants
Type 1 59 (39%) 37 (45%) 12 (29%) 10 (36%) 0.21
Type 2 29 (28%) 2 (13%) 7 (30%) 20 (32%) 0.3

Small for gestational age infants
Type 1 6 (4%) 3 (4%) 1 (2%) 2 (7%) 0.59
Type 2 13 (13%)* 3 (19%) 2 (9%) 8 (13%) 0.65

Neonatal jaundice
Type 1 16 (10%) 10 (12%) 6 (14%) 0 (0%) 0.13
Type 2 10 (10%) 1 (6%) 2 (9%) 7 (11%) 0.85

Caesarian section
Type 1 58 (39%) 33 (41%) 16 (38%) 9 (35) 0.85
Type 2 47 (46%) 7 (44%) 8 (38%) 32 (49) 0.7

Table 3: Perinatal outcome in 155 women with type 1 diabetes and 105 women with type 2 diabetes classified as normal weight, overweight or obese based on prepregnancy BMI. Numbers are given as mean ±SD or number (%). P-value denotes difference across the BMI categories. Chi-square test or unpaired t-test were used to compare type 1 diabetes with type 2 diabetes: *P <0.05 **P <0.01 ***P <0.001. Normal weight (prepregnancy BMI <24.9 kg/m2), overweight (25.0-29.9) or obese (≥30.0).

When comparing women with prepregnancy BMI 25.0-29.9 kg/m2, followed at our center before and after the implementation of our revised local weight gain guidelines in January 2013, we found comparable gestational weight gain (13.7 ± 7.1 vs. 14.1 ± 8.1 kg, P=0.84).

No associations between maternal prepregnancy BMI and offspring birth weight and birth weight SD-score were found when adjusting for HbA1c, excessive gestational weight gain, parity, ethnicity, smoking and diabetes type (Table 4). HbA1c in late pregnancy, type 1 diabetes and multiparity were independent positive predictors of offspring birth weight and birth weight SD-score.

Dependent variables
In both women with type 1 and type 2 diabetes the prevalence of small for gestational age infants were close to the expected 10% in healthy women. The slightly higher prevalence of small for gestational age infants in women with type 2 diabetes was not related to ethnicity (data not shown).

Discussion

In women with pregestational diabetes prepregnancy BMI was not associated with offspring birth weight when adjusted for both glycemic control and other confounders. Independent positive predictors of offspring birth weight were HbA1c in late pregnancy, type 1 diabetes and multiparity.

Our study is according to our knowledge the first to investigate the impact of maternal prepregnancy BMI on offspring birth weight in women with pregestational diabetes, including women with type 2 diabetes, with adjustment for the possible impact of gestational weight gain and maternal glycemic control. Strengths of this study are the inclusion of all consecutive pregnant women with both type 1 or type 2 diabetes, only few exclusion criteria, and the structured prospective collection of clinically relevant data which can be difficult to obtain in large register studies. However, inclusion of a larger sample size in each BMI category and detailed information on the use of antihypertensive treatment during pregnancy would have been desirable. Furthermore maternal weight was given as whole numbers where figures with decimals might have improved the classification of the women in each BMI category. The self-reported prepregnancy weight correlated well with the first weight measurement in pregnancy with an average difference of 2.3 kg and the self-reported prepregnancy weight might therefore be appropriate to use as the time of first pregnancy visit vary several weeks, even though it is self-reported.

Our findings suggest that in women with diabetes, prepregnancy BMI does not predict offspring birth weight in a clinically significant way, in contrast to results seen in healthy women [7,11]. This might be due to the strong influence of glycemic control on fetal growth in women with diabetes [3,8,13,14] overruling other predictors. However, an association between maternal prepregnancy BMI and offspring birth weight might be found in future studies including larger numbers and when maternal glucose control hopefully will be closer to our treatment goals.

This study demonstrates how difficult it is to restrict gestational weight gain in an unselected population of women with diabetes. More than half of the included women, regardless of diabetes type, had excessive gestational weight gain without change after implementation of the new stricter local guideline in January 2013. The reason may be that limiting gestational weight gain is difficult to obtain when the focus is on maintaining strict glycemic control. Furthermore, implementation of a new guideline takes time. As is the case for healthy obese women [23,24] more intervention studies in restricting gestational weight gain in women with diabetes regardless of prepregnancy BMI are needed.

Glucose crosses the placental barrier easily and in women with diabetes [9] elevated maternal glucose level leads to an increased fetal glucose supply. The subsequent elevated fetal glucose level results in fetal hyperinsulinemia and accelerated fetal growth of both lean and fat mass [10]. In women with diabetes and insulin resistance excessive food intake leading to excessive weight gain may result in even higher plasma levels of all nutrients including glucose, amino acids and lipids in comparison to healthy women. These substances cross the placenta resulting in more fat accumulation in infants of mothers with diabetes compared to healthy women [25-27].

In the present study women with type 1 diabetes were not as successful in restricting gestational weight gain as women with type 2 diabetes. Gestational weight gain was approximately 3 kg higher in women with type 1 diabetes compared to women with type 2 diabetes. In line with this women with type 1 diabetes gave birth to infants with a higher offspring birth weight compared to women with type 2 diabetes, despite comparable HbA1c levels. Several factors may contribute to the difference in gestational weight gain. In women with type 2 diabetes weight restriction is the golden standard of treatment and intuitively important for the women and caregivers, also during pregnancy. In addition food intake due to episodes of mild hypoglycemia is more common in women with type 1 diabetes [21]. An intake of 20-40 grams of extra carbohydrate daily, to prevent or treat hypoglycemia four times weekly, leads to an extra weight gain of approximately 2-4 kilos during 40 weeks of pregnancy.

The positive associations between offspring birth weight and HbA1c in late pregnancy, multiparity and type 1 diabetes are well known [3,8,12-14].
An association between gestational weight gain and offspring birth weight in women with pregestational diabetes has been found in previous studies focusing on either type 1 or type 2 diabetes [15,16,18], but this was not confirmed in this study of a combined cohort of women with pregestational diabetes.

To conclude, prepregnancy BMI in women with pregestational diabetes was not independently associated with offspring birth weight. HbA1c in late pregnancy, type 1 diabetes and multiparity were independent positive predictors of offspring birth weight. Women with type 1 diabetes had higher gestational weight gain and offspring birth weight compared to women with type 2 diabetes.

References