β-cell dysfunction in women with previous gestational diabetes is associated with visceral adipose tissue distribution

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Abstract

Context: Glucose intolerance in pregnancy predicts an increased risk of future type 2 diabetes.

Objective: The aim of the study was to evaluate glucose metabolism in women with and without gestational diabetes mellitus (GDM) at 5 years follow-up and identify risk factors associated with disturbed glucose metabolism post-partum.

Design: This follow-up study included 300 consecutively enrolled women from a previous population-based cohort study. The participants underwent oral glucose tolerance test under pregnancy and in the follow-up study, in addition to dual-energy X-ray absorptiometry in the follow-up study.

Results: Fifty-two women (17.7%) were found to have GDM in pregnancy with an odds ratio of 4.8 developing prediabetes 5 years later. β-cell function, but not insulin resistance or sensitivity, was reduced in the follow-up study after adjusting for known risk factors. Furthermore, visceral fat content at follow-up was increased in GDM women compared to non-GDM women, and the β-cell function declined with increasing visceral fat in both groups but was more pronounced in the women with previous GDM.

Conclusions: Women with GDM are at increased risk of developing prediabetes and have a decreased β-cell function 5 years post-partum that is associated with increased visceral fat mass.

Introduction

Women with a history of previous gestational diabetes mellitus (GDM) are at increased risk of future impaired glucose tolerance with some studies reporting a sevenfold increased risk of developing type 2 diabetes (1). However, also women with milder glucose intolerance, but without the diagnosis of GDM, have an increased risk of developing prediabetes and type 2 diabetes in the future (2, 3). Prediabetes is an intermediate form of dysglycemia and identifies individuals at risk of diabetes, cardiovascular (CV) disease and mortality (4, 5, 6). The prevalence of prediabetes increased from 27.4% in 1999 to 2002 and from 34.1% in 2007 to 2010 (7) implying that this is an important group for risk modification.

During pregnancy there is a uniform 50–60% decrease in insulin sensitivity with progression of gestation (8). GDM is a disease of the pancreatic β-cells, which produce inadequate amounts of insulin to meet the increased insulin needs of late pregnancy (9). Many women with GDM seem to have a β-cell defect that is chronic rather than acquired during pregnancy (9). Longitudinal studies of glucose regulation after GDM reveal falling β-cell compensation for chronic insulin resistance, which
might also worsen over time (10). Risk factors for attenuated β-cell function that cause type 2 diabetes include weight gain, insulin resistance, rising levels of C-reactive protein and falling levels of adiponectin (11). Weight loss through dietary intervention and/or physical exercise may improve adipose tissue distribution and provide protection against development of type 2 diabetes following GDM (9).

As follow-up of women with a history of GDM and pre-diabetes states are crucial for targeted intervention to prevent development of overt type 2 diabetes, it is important to determine early predictors of these complications in normal pregnancies. Several studies demonstrate increased BMI during long-term follow-up in women with previous GDM. However, there are no studies investigating specific adipose tissue distribution and associations with indices of glucose metabolism. Recently, a new dual-energy X-ray absorptiometry (DXA) application for quantifying visceral adipose tissue (VAT) in the android region of the body was developed (12). This allowed us to measure total body composition and VAT in a population of women 5 years after the index pregnancy in a simple and cost-effective manner.

The STORK study (STORke barn og Komplikasjoner, translated as Large Babies and Complications) is a prospective cohort study performed in the period between 2002 and 2008 following 1031 Norwegian healthy pregnant women. The follow-up study was performed 5 years after the index pregnancy in 300 women. The aims of the study was to i) investigate the association of GDM (with the new IADPSG criteria) in pregnancy with indices of glucose metabolism and rates of prediabetes after 5 years follow-up, and ii) evaluate visceral fat distribution, and association with indices of glucose metabolism, in GDM vs non-GDM at follow-up.

Subjects and methods

Study design and subjects

The STORK study is a prospective cohort study with a longitudinal design including 1031 healthy women of Scandinavian heritage who gave birth at Oslo University Hospital, Rikshospitalet between 2002 and 2008. Exclusion criteria were multiple pregnancies, known pre-gestational diabetes and severe chronic diseases (lung, cardiac, gastrointestinal or renal), and pregnancies with fetal malformations discovered at the routine scan in week 18 of pregnancy. Details about the study have been published (13). The follow-up study was performed 5 years after the index pregnancy and 300 women participated (Fig. 1). All 1031 participants from the STORK study got an invitation letter. Exclusion criteria were pregnancy and last birth had to be at least 1 year ago. Written informed consent was obtained from all participants in the study. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the Regional Committee for Medical Research Ethics, Southern Norway, Oslo, Norway.

Each pregnant woman had four antenatal visits, gestational age (GA) 14–16, 22–24, 30–32 and 36–38 weeks. Clinical data and blood samples were collected at each visit and stored at $-80^\circ$ C. Parity was divided into primipara for nulliparous women and multipara for those with one or more previous births. Birth weight and placental weight was measured by the midwife within 1 h after the delivery. BMI (kg/m$^2$) was calculated by height and weight. Weight was measured by a calibrated scale at each visit. Height were self-reported at antenatal GA visit 14–16 weeks and measured at the follow-up visit. Gestational weight gain was calculated as the difference between weights measured at antenatal GA visit 36–38 and 14–16 weeks. Total body composition was determined by DXA (GE Lunar Prodigy Densitometer (Software version 12.10; GE Medical Systems, Lunar Corp., Madison, WI, USA)) for the 300 participants at the follow-up visit. No hardware changes were made during the study period, but two upgrading Software version (12.10 and 12.20) were used. In the end of the study, all scans were imported into an updated version of the Software (enCORE 14.10,
GE Medical Systems) and reanalyzed. Standard imaging and positioning protocols were used to scan the subjects. All scans were performed by the same densitometer technologist. CoreScan computes VAT within the android region, located over the abdomen, of a total body DXA scan. CoreScan has been validated against volumetric computed tomography (12, 14). For measuring android fat, a region of interest (ROI) was defined with the caudal limit at the top of the iliac crest and the cephalic limit at the base of the skull. The height of the android ROI was automatically set to 20% of the distance from the iliac crest to the base of the skull. Android ROI contains both visceral (VAT) and subcutaneous adipose tissue (SAT). The CoreScan algorithm works through detection of two key parameters: the width of the SAT layer on the lateral aspects of the abdomen, and the anterior–posterior thickness of the abdomen, which can be attained using the DXA tissue attenuation image. The software estimates the quantity of SAT in the android ROI. VAT was computed by subtracting android SAT from the total android fat. The fat mass data from DXA was transformed to volume using a constant correction factor (0.94 g/cm³) consistent with the density of adipose tissue (12). All VAT under 50 g was set to 50 g since the DXA measurement is unreliable in the low range visceral fat content (precision error (with the iDXA) is ~50 g) (15). The short- and long-term coefficients of variation for our densitometer are 0.8 and 1.4% respectively.

Laboratory measurements

All oral glucose tolerance tests (OGTTs) were performed in the morning after an overnight fast at antenatal visit GA 30–32 weeks and follow-up visit. Venous EDTA blood was analyzed on site by the Accu-Check Sensor glucometer (Roche Diagnostics). Venous blood was also drawn in gel tubes, allowed to clot for 30 min, thereafter centrifuged for 10 min at 3000 g, serum separated and stored at −80°C. Glucose was measured from frozen serum samples at antenatal visit GA 30–32 weeks, with the hexokinase method at an accredited clinical chemistry laboratory at Oslo University Hospital, Rikshospitalet (Hitachi Modular P800 with reagents from Roche) and results are used further for this study. The median difference in glucose values for the 300 women at antenatal visit GA 30–32 weeks between on-site measurements (16) and the measurements performed at the clinical chemistry laboratory was 0.09, 0.17, 0.24, 0.19 and 0.21 mmol/l for the timepoints 0, 30, 60, 90, 120 min in the OGTT test, respectively, and highly correlated $R^2=0.70, 0.84, 0.90, 0.91, 0.90$, consistent with what others have found (17). For the follow-up visit, we used the glucose data from the Accu-check Sensor glucometer. Insulin samples were assayed in duplicate (RIA, DPC, Los Angeles, CA, USA) as previously reported (16) and the same method was used for the follow-up samples.

Diagnosis of GDM and prediabetes

GDM was diagnosed with the IADPSG criteria; fasting plasma glucose (FPG) 5.1–6.9 mmol/l, 1-h plasma glucose ≥10.0 mmol/l or 2-h plasma glucose 8.5–11.0 mmol/l following a 75 g oral glucose load (18). Prediabetes was diagnosed at follow-up visit with the criteria of FPG 5.6–6.9 mmol/l or 2-h plasma glucose 7.8–11.0 mmol/l after 75 g OGTT (19). GDM (IADPSG) and prediabetes were diagnosed after the study was finished. The women who were diagnosed with GDM during pregnancy (WHO) did not get any medication but did receive nutrition guidance.

Insulin sensitivity was measured with the Matsuda index $10000/\sqrt{\text{fasting glucose (mmol/l)} \times \text{fasting insulin (mU/l)}}$, consistent with the density of adipose tissue (12). All VAT under 50 g was set to 50 g since the DXA measurement is unreliable in the low range visceral fat content (precision error (with the iDXA) is ~50 g) (15). The short- and long-term coefficients of variation for our densitometer are 0.8 and 1.4% respectively.

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Statistical analysis

Statistical analyses were conducted using SPSS for Windows, version 21.0. Data are expressed as mean ± s.d. when normally distributed and median (25th, 75th percentile) when skewed. Comparison between women with GDM and non-GDM were performed using χ2-test or Mann–Whitney’s U depending on distribution, and χ2 test for categorical variables. Univariate and stepwise (probability of F to-enter 0.1 – remove 0.15) linear regression analyses were carried out on log transformed variables (if skewed) and results are given as standardized regression coefficients. Interactions between VAT and indices of glucose metabolism were evaluated by univariate general linear model with glucose indices as dependent and VAT, glucose indices, GDM and the interaction term...
(VAT×GDM) as independent variables. <0.05 were considered significant.

Results

A comparison of the 300 women included with the 731 women who did not participate in the follow-up study showed no significant difference between the two groups in terms of BMI, blood pressure (BP), family history of diabetes, smoking, parity, glucose tolerance (calculated based on Accu-check blood glucose measurements) and GDM proportion. The women who did participate were older (mean ± s.d. 32.2 ± 3.9 vs 30.9 ± 3.8, P=0.013).

Comparison between GDM and non-GDM group in pregnancy and 5 years follow-up.

Table 1 shows the characteristics of the study population at pregnancy and at follow-up 5 years later stratified into the groups of GDM (n=52) and non-GDM (n=248). The proportion of GDM with the new IADPSG criteria was 17.7% (calculated based on complete OGTTs). 11.3% were diagnosed with GDM based on the old WHO criteria giving a 1.6-fold increase in the prevalence of GDM with the new criteria. At pregnancy the GDM group was older, had a higher BMI, and a higher placenta and birth weight of the child. As expected, they had higher levels of glucose and insulin during OGTT (except insulin 30 min). Gestation age or parity during pregnancy was not different between the groups. There was no difference in follow-up time between the groups, and at 5 years following pregnancy, GDM women were older, had a higher BMI, and levels of glucose and insulin during OGTT (except insulin 30 min) compared to initially non-GDM women. Since nutritional guidance was given to those classified by the old WHO criteria, but not those newly classified as GDM by IADPSG we compared weight gain during pregnancy in these groups. We found a smaller weight gain in guided patients (median (25th, 75th percentile): 9.5 (6.3, 11.4) kg) compared to non-GDM women (10.2 (8.2, 12.7) kg) P=0.044, while no differences were observed between untreated GDM (10.3 (8.4, 14.8) kg) and non-GDM women: P=0.362. However with regard to the outcome variables below, no associations were observed between weight gain during pregnancy and insulin resistance (r=0.04, P=0.56), insulin sensitivity (r=0.01, P=0.81), β-cell function (r=0.05, P=0.39) or VAT fat volume (r=0.06, P=0.31) at follow-up in the population as a whole or within the groups (P values between 0.16 and 0.90).

The proportion of prediabetes in the follow-up study was 6.7%, 17.3% of the GDM subjects and 4.2% of the non-GDM subjects had prediabetes (including one subject with type 2 diabetes from the GDM group) at the follow-up visit (P<0.001). Thus, the GDM women had a 4.8 (1.8–12.5), P<0.001 (OR (95% CI)), times higher frequency of developing prediabetes 5 years later compared to women with a normal glucose tolerance in pregnancy.

Indices of glucose metabolism in GDM in pregnancy and at 5 years follow-up

As shown in Table 1, peripheral insulin sensitivity and β-cell function was significantly decreased in GDM compared to non-GDM at weeks 30–32 (P<0.001, P<0.001, and P=0.001 respectively), while HOMA-IR was increased (P<0.001). Adjusting for differences in age, smoking, family history of diabetes, parity, and BMI between GDM and non-GDM group, insulin sensitivity, β-cell function and HOMA-IR were still different between the groups (P<0.001).

At the follow-up visit, insulin sensitivity and β-cell function were still decreased in the GDM group (P<0.001) and HOMA-IR was increased (P=0.003). However, adjusting for age, smoking, follow-up time, family history of diabetes, parity, and BMI, only β-cell function was still significantly different (P=0.017) between the GDM and non-GDM women.

Visceral fat is increased in women with previously GDM and correlated with β-cell function

We next investigated the association between VAT and indices of glucose metabolism at follow-up. First, we found visceral fat content to be higher in women with previous GDM compared to previous non-GDM women (Table 1, P<0.001). Further, as shown in Table 2, we found a strong correlation between VAT and insulin resistance, insulin sensitivity and β-cell function in univariate analysis. In multivariable regression, BMI, VAT and family history of diabetes were predictors of insulin sensitivity and insulin resistance. In addition to the preceding predictors, also systolic BP and previous GDM were significant predictors of β-cell function. Finally, when comparing regression lines between visceral fat and insulin resistance, insulin sensitivity and β-cell function between GDM and non-GDM groups, a trend towards an interaction between GDM and VAT on β-cell function was observed, with a steeper slope in women with previous GDM (non-GDM: B = −0.36 ± 0.05, GDM: B = −0.59 ± 0.13, P=0.08). No differences were seen.
between the slopes of the regression lines between visceral fat, insulin resistance \((P=0.61)\) and insulin sensitivity \((P=0.38)\) between GDM and non-GDM groups.

**Discussion**

In this study, we investigated glucose metabolism in pregnancy and follow-up in GDM women 5 years after the index pregnancy, compared to non-GDM women. Our main findings were that \(\beta\)-cell function was decreased in GDM women at follow-up, also after adjustment for differences in BMI. Visceral fat content was elevated in previous GDM women, with a strong association to low \(\beta\)-cell function, indicating that this fat compartment may contribute to metabolic disturbances during long-term follow-up.

We found 17.7% women with GDM based on the IADPSG criteria. However, while the current IADPSG recommend standardizing the OGTT test at week 24–28, our study started prior to this recommendation and included an early (14–16 weeks) and a late (30–32 weeks) OGTT measurement in the protocol. This could potentially influence the prevalence of GDM detected in our study. However, our results are comparable to the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (23, 24) and a population-based study from Oslo where the Western Europe group had a GDM prevalence of about 24% (17). Furthermore, in the same study 6.7% had developed prediabetes 5 years after the index pregnancy. In a Finnish retrospective study, ~48% of the GDM women and 26% of the controls were diagnosed with prediabetes 7.3 (5.3 s.d.) years later (25). Despite that the

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**Table 1** Characteristics of the study population. Data given as mean ± s.d. when normal distributed and median (25th, 75th) when skewed distributed. Comparison between women with GDM and non-GDM were performed using \(t\)-test for normal distributed variables, Mann–Whitney’s \(U\) for non-distributed continuous variables, and \(\chi^2\) test for categorical variables.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (week 30–32)</th>
<th>Follow up (5 years follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GDM</td>
<td>Non-GDM</td>
</tr>
<tr>
<td>(n)</td>
<td>52</td>
<td>248</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)(^a)</td>
<td>33.4 ± 4.4</td>
<td>32.0 ± 3.7*</td>
</tr>
<tr>
<td>Height (cm)(^a)</td>
<td>169 ± 6</td>
<td>169 ± 6</td>
</tr>
<tr>
<td>Gestation length (weeks)</td>
<td>40.4 (39.0, 41.4)</td>
<td>40.3 (39.2, 41.0)</td>
</tr>
<tr>
<td>Placenta weight (g)</td>
<td>790 (700, 900)</td>
<td>700 (600, 810)*</td>
</tr>
<tr>
<td>Birth weight of the child (g)</td>
<td>3810 ± 540</td>
<td>3596 ± 518*</td>
</tr>
<tr>
<td>Family history of diabetes (%)</td>
<td>1.9/26.9</td>
<td>2.9/16.6</td>
</tr>
<tr>
<td>Smoking current/previous (%)</td>
<td>1.15 (105, 120)</td>
<td>110 (105, 120)</td>
</tr>
<tr>
<td>Systolic blood pressure (DBP) (mmHg)</td>
<td>70 (60, 70)</td>
<td>70 (60, 70)</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.4 (4.2, 6.4)</td>
<td>4.4 (4.2, 6.4)</td>
</tr>
<tr>
<td>Glucose 30 min (mmol/l)</td>
<td>8.8 (8.4, 9.7)</td>
<td>7.3 (6.5, 8.1)</td>
</tr>
<tr>
<td>Glucose 60 min (mmol/l)</td>
<td>10.2 (8.8, 10.9)</td>
<td>7.1 (5.9, 8.1)</td>
</tr>
<tr>
<td>Glucose 90 min (mmol/l)</td>
<td>8.9 (7.8, 10.2)</td>
<td>6.3 (5.1, 7.3)</td>
</tr>
<tr>
<td>Glucose 120 min (mmol/l)</td>
<td>7.6 (6.4, 8.8)</td>
<td>5.8 (4.8, 6.5)</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>60 (45, 85)</td>
<td>36 (25, 54)</td>
</tr>
<tr>
<td>Insulin 30 min (pmol/l)</td>
<td>466 (294, 563)</td>
<td>403 (271, 558)</td>
</tr>
<tr>
<td>Insulin 60 min (pmol/l)</td>
<td>589 (415, 840)</td>
<td>448 (310, 628)</td>
</tr>
<tr>
<td>Insulin 90 min (pmol/l)</td>
<td>605 (422, 903)</td>
<td>383 (252, 581)*</td>
</tr>
<tr>
<td>Insulin 120 min (pmol/l)</td>
<td>528 (313, 802)</td>
<td>325 (216, 471)*</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>63 (46, 90)</td>
<td>123 (85, 182)</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>2.01 (1.29, 2.74)</td>
<td>1.00 (0.69, 1.53)</td>
</tr>
<tr>
<td>(\beta)-cell function</td>
<td>549 (458, 653)</td>
<td>997 (773, 1286)</td>
</tr>
<tr>
<td>Body composition/weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain during pregnancy</td>
<td>28.1 (26.7, 30.1)</td>
<td>26.2 (3.7, 28.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>80.3 (73.5, 88.5)</td>
<td>74.2 (68.3, 81.1)</td>
</tr>
<tr>
<td>Visceral fat volume (cm³)</td>
<td>309 (193, 888)</td>
<td>140 (53, 345)</td>
</tr>
</tbody>
</table>
women in our study were characterized by attenuated β-cell function at follow-up, there was a low number of GDM women who developed prediabetes 5 years after pregnancy. This could partly be explained by the substantial loss of β-cell compensation that is needed to raise glucose levels to the diabetic range (9). In addition, we did not measure HbA1c, which in some studies has been shown to be a good predictor of future diabetes and could identify additional women with prediabetes (26).

Women with previous GDM had lower insulin sensitivity and β-cell function and a higher insulin resistance compared with previous non-GDM women 5 years after the index pregnancy. However, after adjusting for known risk factors including BMI at follow-up, only β-cell function remained significantly decreased in GDM women. A recent study demonstrated a greater worsening of β-cell function from 3 months to 3 years in previous GDM compared to a reference group (27), while another study suggested that β-cell function improved over time after a GDM pregnancy (28). Of interest, Li et al. (29) found that in diabetic women with a history of GDM, women who were non-obese before pregnancy and post-partum displayed the most β-cell dysfunction, while non-obese women who markedly increased their BMI displayed the highest insulin resistance. Thus, β-cell dysfunction may be a stronger contributor to diabetes risk among normal weigh women with previous GDM. However, with regard to verifying the findings from these studies in our population, we are limited by not having similar data on these indices of glucose metabolism early after pregnancy and can therefore not address the longitudinal changes in β-cell function post-partum. In addition, our study is too small to evaluate the impact of changes in BMI, β-cell dysfunction and incidence of prediabetes/diabetes.

A major finding in the present study was the increased visceral fat volume at follow-up in women with previous GDM. The increase in visceral fat is a volumetric measure and is thus not only due to a higher BMI or in general adipose tissue mass in these women, but reflects a different fat distribution than in non-GDM women. Importantly, previous GDM and visceral fat volume were strong independent predictors, in addition to BMI, of β-cell dysfunction 5 years later. A recent study showed that women with previous GDM have faster deterioration of β-cell function than women without a history of GDM, independent of body fat (30). However, these studies did not have visceral fat measurements. Indeed, when comparing the slopes of the regression lines between visceral fat volume and indices of glucose metabolism at follow-up, similar slopes were detected for insulin resistance and sensitivity in GDM and non-GDM women. In contrast, women with previous GDM had a trend towards a steeper slope of the regression line between the visceral fat and β-cell function compared to non-complicated pregnancy. This may suggest that women with previous GDM have more metabolically active fat that may be detrimental to β-cell function. As hormones and cytokines produced and secreted from adipocytes may directly influence these indices of glucose metabolism early after pregnancy and can therefore not address the longitudinal changes in β-cell function post-partum.
function (31), it is tempting to hypothesize that visceral fat inflammation may be crucially linked with pancreatic β-cell dysfunction, as suggested by others (32).

It has been debated if GDM is a chronic disease state that is detected during pregnancy and leads to type 2 diabetes, or whether pregnancy has an adverse long-term effect on insulin resistance. Our data suggest that visceral fat distribution and β-cell function are strongly linked 5 years after the index pregnancy. Thus, important questions in future studies are if the visceral fat content reflects the fat distribution before pregnancy, or if there is a redistribution during or after pregnancy. Insulin resistance during pregnancy could have a deteriorating effect on fat distribution that is difficult to reverse after pregnancy in the women with previous GDM, but it could also be that increased visceral fat prior to pregnancy speeds up the process of β-cell dysfunction during pregnancy. A recent study in 407 Danish women with GDM assessed 3 month post-partum identified an association between GAD autoantibodies positivity and impaired β-cell function (33) and it would be interesting to see if this influenced the association we found between VAT fat mass and β-cell function in our study. However, they found a prevalence of 5.4% for GAD antibody positivity and since our study had 52 women with GDM, the influence of GAD in this setting would be better addressed in future larger studies on long-term metabolic complications in GDM women.

Strengths of our study include a well-characterized population based cohort, with similar follow-up time between the GDM and non-GDM group. However, the follow-up percent was relatively low and could represent a bias. This could be partly explained by that some of the younger women were pregnant and could not participate, thus participants in the follow-up study were older than the women who did not participate. Finally, although the method for estimation of VAT has been validated against computer tomography, the gold-standard for assessment of VAT, a recent study reported a decreasing precision error with increasing BMI and that a higher coefficient of variation was observed for normal BMI (34).

In conclusion, a poorer β-cell function in women with previous GDM is strongly linked to increased visceral fat content, suggesting the visceral fat may be more harmful for women with previous GDM than women with uncomplicated pregnancies.

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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