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Long-term maternal metabolic and cardiovascular phenotypes after a pregnancy complicated by mild gestational diabetes mellitus or obesity

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Abstract

Objective: To evaluate the association of mild gestational diabetes (GDM) and obesity with metabolic and cardiovascular markers 5-10 years after pregnancy.

Study Design: This was a secondary analysis of 5-10 year follow-up study of a mild GDM treatment trial and concurrent observational cohort of participants ineligible for the trial with abnormal 1-hour glucose challenge test only. Participants with 2-hour glucose tolerance test at follow-up were included. The primary exposures were mild GDM and obesity. The outcomes were insulinogenic index (IGI), 1/HOMA-IR, and cardiovascular markers VEGF, VCAM-1, CD40L, GDF-15, and ST-2. Multivariable linear regression estimated the association of GDM and obesity with biomarkers.

Results: Of 951 participants in the parent study, 642(68%) were included. Lower 1/HOMA-IR were observed in treated and untreated GDM groups, compared with non-GDM (mean differences −0.24, 95%CI −0.36–−0.12 and −0.15, 95%CI −0.28–−0.03, respectively). Lower VCAM-1 (angiogenesis) was observed in treated GDM group (mean difference −0.11, 95%CI −0.19–−0.03). GDM was not associated with IGI or other biomarkers. Obesity was associated with lower 1/HOMA-IR (mean difference −0.42, 95%CI −0.52–−0.32), but not other biomarkers.

Conclusion: Five to ten years after delivery, prior GDM and obesity are associated with more insulin resistance but not insulin secretion or consistent cardiovascular dysfunction.

Keywords

cardiovascular disease; diabetes; gestational diabetes; obesity; pregnancy

INTRODUCTION

Gestational diabetes mellitus (GDM) is associated with significant maternal and infant morbidity[1,2] as well as increased lifetime risk for maternal type 2 diabetes (T2DM) and cardiovascular disease.[3,4] Diabetes is a metabolic disease characterized by hyperglycemia due to relative insulin insufficiency. Insulin insufficiency can result from either impaired insulin production and secretion from the pancreatic β-cells, impaired insulin sensitivity at target tissues, or both. Increased insulin production can compensate for decreased insulin sensitivity in a hyperbolic relationship, and thus the combination of the two indices have been shown to differ among individuals with normal glucose tolerance, impaired glucose tolerance, and T2DM.[5,6] In pregnancy, obese patients are twice as likely to have impaired insulin sensitivity, compared with those with normal BMI,[7] but patients with both GDM and impaired insulin production are at the highest risk for overt T2DM later in life.[8] Long term follow-up to define the maternal metabolic phenotype years after a pregnancy complicated by GDM has received less attention.

Persistent hyperglycemia after pregnancy can cause inflammation and endothelial activation, leading to central arterial stiffening and development of cardiovascular disease later in life.[9] Inflammation and endothelial activation can be measured using VEGF (angiogenic growth factor), VCAM-1 (endothelial activation), and CD40 Ligand (platelet release/inflammation).[10-12] Additionally, biomarkers such as GDF-15 and ST-2 have been associated with new onset atherosclerosis and heart failure and have been used to help determine prognosis and predict mortality in addition to traditional risk factors.[10-12] Treatment of hyperglycemia has been shown to improve vascular function and reduce soluble markers of endothelial dysfunction,[13] however the long-term effect of GDM treatment has not been well characterized.

The primary objectives of this study were to define the prevalence of maternal β-cell dysfunction and insulin resistance 5-10 years after mild GDM and to evaluate the association of mild GDM (treated and untreated) and separately obesity with long-term β-cell dysfunction, insulin resistance, and cardiovascular disease.

MATERIALS AND METHODS

This was a secondary analysis of data and biospecimens collected during a 5-10 year follow-up study of participants enrolled in a mild GDM treatment trial and participants ineligible for the trial who were enrolled in a concurrent observational study conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network.[14,15] A complete description of the study design, methodology and results of the treatment trial[16] and 5-10 year follow-up study[17,18] have been previously published. Briefly, the GDM treatment trial enrolled participants with mild GDM defined as a normal fasting glucose < 95 mg/dL but two of the three post-100g glucose load measurements meeting Carpenter-Coustan criteria (1-hour ≥ 180 mg/dL, 2-hour ≥ 155 mg/dL, and 3-hour ≥ 140 mg/dL). Enrolled participants were randomized to routine prenatal care or treatment including nutritional counseling and insulin if required. Following delivery, participants were notified of their glucose tolerance tests and advised to have a 2-hour oral glucose tolerance test at their 6 week postpartum visit and fasting glucose surveillance annually. The 5-10 year follow-up study included participants from the mild GDM treatment trial as well as a concurrent observational cohort of participants who were ineligible for participation in the trial with abnormal 1-hour glucose challenge test (135 to 200 mg/dL) but normal 100g 3-hour oral glucose tolerance test results. The follow-up study was performed from February 2012 to September 2013 and included 12 of 16 centers who had participated in the GDM treatment trial and were still members of the MFMU Network at the time of the follow-up study (94% of the original participants eligible). For the follow-up study, participants were contacted 5-10 years after the index pregnancy, and those who chose to participate were instructed to fast for at least 6 hours prior to their study visit at which time a 2-hour 75-g oral glucose tolerance test was performed if they were not already being treated for T2DM. Fasting insulin levels were measured, and additional blood was collected at 1 and 2 hours for future analysis. Trained and certified research personnel abstracted data from the original study charts as well as at the follow up visit including demographic information, medical history, and maternal and neonatal outcomes.

For this secondary analysis, participants were included if they had both fasting and 1-hour blood collected during the 2-hour oral glucose tolerance test at the 5-10 year follow-up visit. Participants who did not complete glucose tolerance testing because they were pregnant or had a diagnosis of T2DM at the time of the 5-10 year follow-up visit were not included in this analysis. Participants who were missing data for key covariates (OGTT results from GDM treatment trial, race/ethnicity, maternal age, BMI in index pregnancy and at time of follow-up, baseline blood pressure, hypertension in index pregnancy, chronic hypertension at time of follow-up) were also excluded.

Our primary outcome was the insulinogenic index (IGI), a measure of pancreatic ß-cell insulin secretion, that was calculated as Δ insulin / Δ glucose from fasting and 1-hour maternal serum concentrations. Secondary outcomes included 1/Homeostatic model assessment of insulin resistance (HOMA-IR) that was calculated as 1/[22.5 x 18 / blood glucose (mg/dl) x insulin (μU/mL)] as well as cardiovascular markers VEGF, VCAM-1, CD40L, GDF-15, and ST-2 (Table 1). VEGF and VCAM-1 are markers of angiogenesis and endothelial activation whereas CD40L is a measure of platelet release and inflammation. GDF-15 is a marker of apoptosis and oxidative stress, and ST-2 has been shown to predict mortality and heart failure.[10-12]

Maternal serum was analyzed using customized, magnetic bead-based multiplex assays for the Luminex® platform. The Luminex® assays were previously validated for use and tested for sensitivity, intra-assay precision, and inter-assay precision to ensure assay linearity. Antibody pairs were selected for the target biomarkers (insulin, VEGF, VCAM-1, CD40L, GDF-15, and ST-2) and 0.5 μL serum aliquots for eligible participants were thawed and processed according to manufacturer's kit instructions (R&D Systems, Minnesota, USA). The analysis was performed using flow-cytometry hardware in the Cytokine and Biomarker Analysis Facility at the University of North Carolina where the laboratory technicians were blinded to parent study GDM group and BMI.

The primary exposures of interest are GDM and obesity. Baseline characteristics and maternal biomarkers were compared by index pregnancy GDM status (treated GDM, untreated GDM, and non-GDM) and by index pregnancy obesity status (BMI ≥ 30m/kg^2). The Wilcoxon rank sum test or Kruskal-Wallis test was used for analyzing continuous variables, and the Chi-square or Fisher's exact test was used for analyzing nominal variables. Multivariable generalized linear regression estimated the association of GDM status and obesity with the metabolic and cardiovascular markers, adjusting for age, race/ethnicity, smoking status, and years since index pregnancy. These covariates were chosen *a priori* based on previously published literature. Log-transformed values of VEGF, VCAM-1, CD40L, GDF-15, and ST-2 and z-score transformations of ranked IGI values were used in the linear analysis to approximate normality. Results are presented as adjusted mean differences given that the outcomes of interest are continuous variables without clear, consistent cutoffs to designate normal versus abnormal. Due to the exploratory nature of this analysis, statistical significance was defined as $p<0.05$ without adjustment for multiple comparisons. All tests were two-tailed, and all analyses were performed with SAS (version 9.4). No imputation for missing data was performed.

Approval by the Institutional Review Board was obtained for the original study and the follow-up study at all participating centers. This secondary analysis was approved by the University of North Carolina at Chapel Hill Institutional Review Board (IRB # 19-1432, Approved 6/11/2019).

RESULTS

Of 951 participants in the GDM follow-up study, 642 (68%) participants with serum samples available for testing were included in this analysis (Figure 1). Loss to follow-up did not vary by exposure status. In the index pregnancy, 176 (27%) participants had treatment for GDM, 158 (25%) did not have treatment for GDM, and 308 (48%) did not have GDM. Overall, 301 (47%) participants were obese at parent trial entry. Participants who were treated for GDM were more likely to be older than those who did not have treatment and those who did not have GDM (Table 2). Race and ethnicity, tobacco use, obesity at parent trial entry, and years since the index pregnancy were similar between GDM groups. Women with obesity were more likely to have higher fasting glucose and lower 3-hour glucose on oral glucose tolerance testing and more likely to be Hispanic, compared to women without obesity (Supplemental Table 1).

With regards to the primary and secondary outcomes, there were no significant differences in IGI, VEGF, CD40L, GDF-15, or ST-2 between GDM groups or between obese vs non-obese women in unadjusted analyses (Tables 3 and 4). Women with treated and untreated GDM had lower 1/HOMA, compared to those with non-GDM (adjusted mean differences −0.24, 95%CI −0.36 – −0.12 and −0.15, 95%CI −0.28– −0.03, respectively, Figure 2). Stated otherwise, women with GDM had lower insulin sensitivity and higher insulin resistance, compared to women without GDM. Lower VCAM was also observed in the treated GDM group, compared with non-GDM (adjusted mean difference −0.11, 95%CI −0.19 – −0.03). GDM status was not associated with IGI or other cardiovascular markers (Figure 2). Obesity was associated with lower 1/HOMA (adjusted mean difference −0.42, 95%CI −0.52 – −0.32), but not with IGI or other cardiovascular markers (Figure 3). Results were unchanged when BMI was analyzed as a continuous variable. Additionally, there was no evidence of interaction between GDM group and obesity for the study outcomes. This means that the association between GDM group and the study outcomes did not differ based on whether people were obese or not, and the association between obesity and study outcomes did not differ based on whether people had GDM or not.

DISCUSSION

Compared with participants without GDM, participants with untreated and treated mild GDM were at increased risk for worsening insulin resistance, but not deficient pancreatic β-cell secretion of insulin at 5-10 year follow-up. Participants with treated mild GDM had lower VCAM levels suggestive of less angiogenesis, compared with participants without GDM, but there was no association between mild GDM and other markers of cardiovascular dysfunction at long-term follow-up. Similarly, participants who were obese during the index pregnancy were at increased risk for worsening insulin resistance 5-10 years after delivery,

compared with those who were not obese, but obesity was not associated with deficient pancreatic ß-cell secretion of insulin or cardiovascular dysfunction.

The results of this study confirm and expand upon previously published findings. In another secondary analysis of the GDM follow-up study, less than 10% of participants with mild GDM developed T2DM within 5-10 years, which is lower than the estimated rate for all patients with GDM.[19] Even though only a small proportion of participants with mild GDM developed overt T2DM, we hypothesized there may be differences in pancreatic ß-cell secretion of insulin and insulin resistance that are detectable prior to development of T2DM. For example, a Norwegian study of patients with glucose intolerance during pregnancy demonstrated that pancreatic ß-cell function was reduced 5-years after pregnancies complicated by GDM, compared with those without GDM.[20] In our study, we also found evidence of metabolic dysfunction prior to the development of T2DM, however, we found an association between mild GDM and insulin resistance, rather than differences in insulin secretions from pancreatic ß-cells. Differences in patient population and underlying metabolic phenotype likely explain the discrepancy in our results. Additionally, participants who were diagnosed with T2DM before the 5-10 year follow-up were excluded from our analysis which may bias our results towards the null. With regards to obesity and insulin sensitivity at 5-10 years after pregnancy, our findings are consistent with prior studies that show obese patients have more insulin resistance compared to non-obese patients.[7] This demonstrates that the impact of obesity appears to be similar 5-10 years after delivery as it is during pregnancy.

With regards to cardiovascular disease, participants who had a history of treated GDM compared to those without GDM had a lower VCAM-1, a marker of angiogenesis which can be elevated in the setting of an unstable or ruptured plaque leading to acute coronary syndrome. This was an unexpected finding as previous studies such as the GENetics of Non-Insulin dependent Diabetes (GENNID) study demonstrated that a history of GDM increased the odds of coronary artery disease or stroke 2-fold by 30-years after delivery (aOR 1.85, 95% CI 1.21-2.82), compared to no GDM.[3] Additionally, coronary artery disease was diagnosed approximately 7 years earlier in participants with a history of GDM (45.5 ± 2.2 vs 52.5 ± 1.9 years, p=0.02). We were unable to assess whether the treatment of GDM rather than the history of GDM itself may have played a role in the lower VCAM concentrations. In a Canadian study, a history of GDM was only associated with cardiovascular disease when participants were also overweight (aHR 2.1, 95% CI 1.1-3.5), and not with only a history of GDM (aHR 1.4, 95% CI 1.0-1.9), compared to women who were not overweight with no GDM.[21] In this study the cumulative incidence of cardiovascular disease did not substantially increase until approximately 9 years after delivery.[21] Furthermore, a systematic review and meta-analysis of over 5 million individuals with follow-up up to 25 years after delivery demonstrated a two-fold higher risk of future cardiovascular events after a pregnancy complicated by GDM (RR 1.98, 95% CI 1.57-2.50).[22] Although we did not see significant associations between GDM or obesity and the majority of the cardiovascular biomarkers in this study nor evidence of interaction between GDM and obesity, our follow-up was shorter than these previous studies and excluded women who had developed T2DM since delivery.

Evaluating participants with only mild GDM, rather than evaluating participants representing a range of GDM severity, can be seen as a limitation of this study. Additionally, participants who were diagnosed with T2DM prior to the follow-up study were excluded from this analysis. Our findings apply to individuals with a history of mild GDM or obesity who did not have overt T2DM prior to the 5-10 year postpartum visit and thus, our conclusions may not be generalizable to patients with more severe disease. The magnitude of effect of GDM compared to non-DM may also be lessened given that individuals included in non-GDM group may have had some degree of abnormal metabolism given that they had an abnormal GCT. Although we adjusted for potential confounding baseline characteristics from the index pregnancy, we do not have detailed data about changes that may have occurred during the interval between delivery and follow-up such as lifestyle modification or preventative therapies for glucose intolerance. Lastly, our significant findings should be interpreted carefully as there is a higher probability of false positive findings given the multiple comparisons performed. We felt that multiple comparisons were justified given there is not a single test to assess cardiovascular disease and evaluation of different pathways of cardiovascular dysfunction was desired. Despite these limitations, this study design allowed us a unique opportunity to evaluate the metabolic and cardiovascular status of participants with a history of mild GDM or obesity. Use of biomarkers allowed us to evaluate different etiologies for T2DM (insulin resistance and pancreatic β-cell insulin secretion) as well as cardiovascular disease (endothelial activation, angiogenesis, platelet release and inflammation). The parent study had a precise definition of mild GDM that ensured homogeneity of the disease phenotype studied, but also diversity in racial/ethnic and geographic backgrounds as it enrolled from 12 different centers across the U.S. While we cannot exclude the possibility of selection bias given that only 68% of participants in the follow-up study were included in this analysis and race/ethnicity differed, there were no significant differences in maternal age, GDM status, or BMI in our cohort compared with the parent study as a whole (Supplemental Table 2).

In summary, participants with mild GDM and obese pregnant participants were at increased risk for worsening insulin resistance 5-10 years after the index pregnancy, but not pancreatic ß-cell secretion of insulin. Women with treated mild GDM had biomarkers suggestive of less angiogenesis at long-term follow-up, compared with no GDM, but neither mild GDM nor obesity was associated with other markers of cardiovascular dysfunction. Given these findings and previously reported associations, patients with mild GDM may have a lower risk for development of T2DM or cardiovascular disease compared to historical rates from women with any GDM, or it may occur at a longer interval after delivery. Nonetheless, regular monitoring of patients with a history of GDM for the development of both T2DM and cardiovascular disease is recommended. Future studies are needed to evaluate differences in metabolic and cardiovascular phenotypes among patients across the full spectrum of GDM including those with early GDM diagnosis and those with more severe disease requiring treatment with insulin. Additionally, longitudinal studies are needed to measure metabolic and cardiovascular function before, during and after pregnancy in order to define which interventions are most effective at improving long-term outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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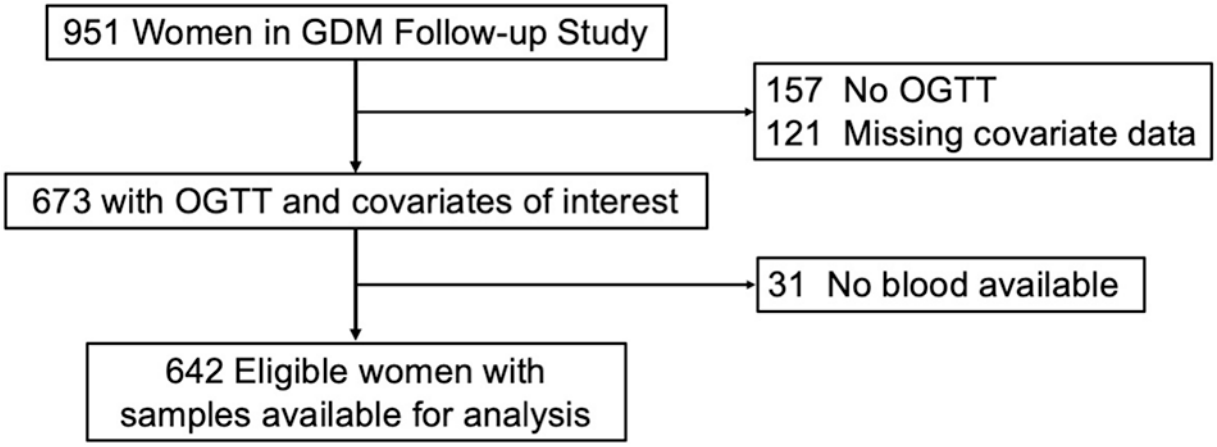

Figure 1.
Flow diagram of study cohort

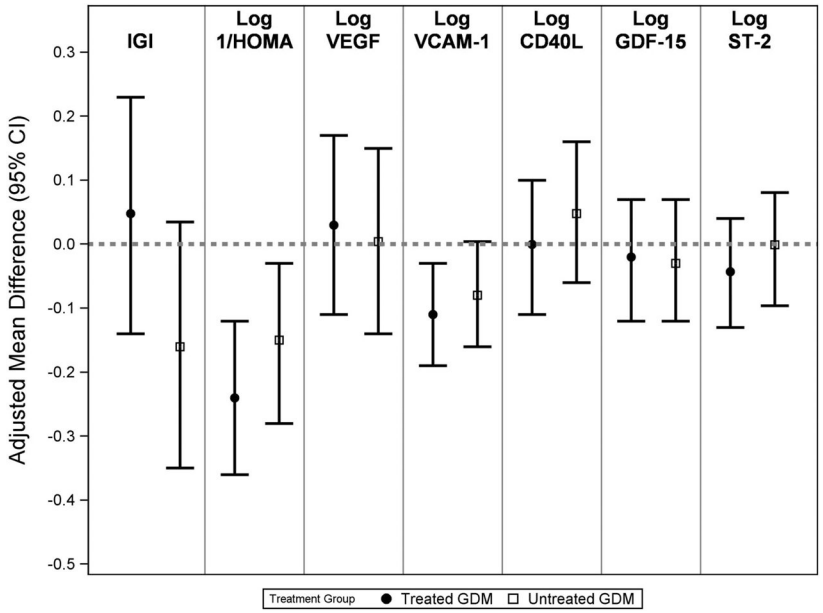

Figure 2.

Adjusted mean difference of metabolic and cardiovascular biomarkers by gestational diabetes mellitus (GDM) group

Footnote: GDM, gestational diabetes mellitus

*Referent=Non-GDM; Adjusted for obesity, age, race/ethnicity, and years since index pregnancy

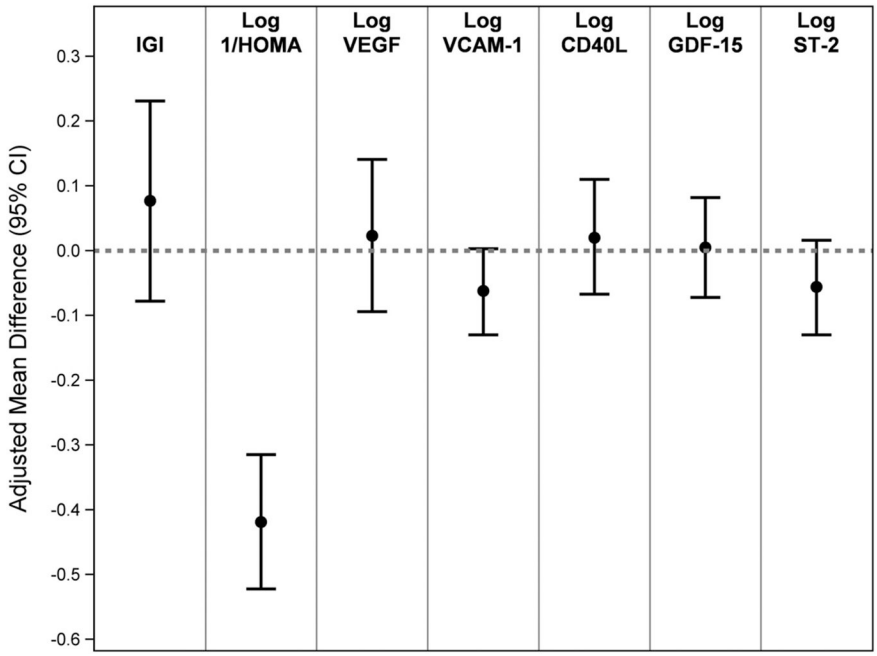

Figure 3.

Adjusted mean difference of metabolic and cardiovascular biomarkers by obesity

[†]Referent=Non-obese, Adjusted for gestational diabetes group, age, race/ethnicity, and years since index pregnancy

Table 1.

Clinical significance of metabolic and cardiovascular biomarkers

Biomarker	Clinical relevance	Interpretation
Insulinogenic index	Pancreatic B-cell production and release of insulin	Lower levels associated with less insulin release
1/HOMA	Insulin sensitivity	Lower levels associated with less insulin sensitivity and more insulin resistance
VEGF	Angiogenic growth factor	Higher levels associated with more disease
VCAM-1	Endothelial activation	Higher levels associated with more disease
CD40L	Platelet release, inflammation	Higher levels associated with more disease
GDF-15	Apoptosis, oxidative stress, ischemia	Higher levels associated with more disease
ST-2	Predictor of mortality and heart failure	Higher levels associated with more disease

Table 2.

Baseline, delivery and follow-up characteristics by baseline gestational diabetes mellitus (GDM) group

	All participants (n=642)	Treated GDM (n=176)	Untreated GDM (n=158)	Non-GDM (n=308)
Baseline characteristics				
Maternal age (years) *	28.3 ± 5.3	29.5 ± 5.0	28.6 ± 5.5	27.5 ± 5.3
Race/ethnicity				
Non-Hispanic Black	70 (10.9)	16 (9.1)	18 (11.4)	36 (11.7)
Non-Hispanic White	218 (34.0)	66 (37.5)	48 (30.4)	104 (33.8)
Hispanic	337 (52.5)	89 (50.6)	87 (55.1)	161 (52.3)
Other	17 (2.7)	5 (2.8)	5 (3.2)	7 (2.3)
Tobacco use at parent trial entry	49 (7.6)	17 (9.7)	10 (6.3)	22 (7.1)
Obese at parent trial entry	301 (46.9)	78 (44.3)	75 (47.5)	148 (48.1)
100 g glucose tolerance test results (mg/dL) *				
Fasting result	86.0 ± 5.7	87.1 ± 5.6	86.4 ± 5.7	85.1 ± 5.6
1-hour result	174.0 ± 30.0	192.1 ± 21.5	194.2 ± 17.3	153.3 ± 25.2
2-hour result	152.2 ± 29.9	171.9 ± 20.8	172.7 ± 19.2	130.5 ± 22.8
3-hour result	123.1 ± 29.4	137.1 ± 29.2	133.6 ± 31.1	109.8 ± 21.8
Hypertensive disease in pregnancy	66 (10.3)	18 (10.2)	18 (11.4)	30 (9.7)
Delivery characteristics				
Gestational age at delivery (weeks)	39.1 ± 1.7	38.9 ± 1.9	39.1 ± 1.6	39.2 ± 1.6
Follow-up characteristics				
Years since index pregnancy	7.0 ± 1.4	7.1 ± 1.4	7.1 ± 1.4	6.9 ± 1.4
Age at follow-up (years) *	35.4 ± 5.6	36.6 ± 5.3	35.9 ± 5.5	34.5 ± 5.6
Number of pregnancies since index pregnancy				
0	300 (46.7)	85 (48.3)	81 (51.3)	134 (43.5)
1	233 (36.3)	59 (33.5)	52 (32.9)	122 (39.6)
2+	109 (17.0)	32 (18.2)	25 (15.8)	52 (16.9)
Number of pregnancies with GDM since index pregnancy *				
0	568 (88.5)	146 (83.0)	137 (86.7)	285 (92.5)
1	64 (10.0)	25 (14.2)	19 (12.0)	20 (6.5)
2+	10 (1. 6)	5 (2.8)	2 (1.3)	3 (1.0)
Obese at follow-up	256 (39.9)	65 (36.9)	65 (41.4)	126 (40.9)
Tobacco use at follow-up	54 (8.4)	16 (9.1)	14 (8.9)	24 (7.8)
Chronic hypertension	36 (5.6)	10 (5.7)	11 (7.0)	15 (4.9)

* $p<0.001$ for maternal age at baseline and follow-up, baseline OGTT results; $p=0.02$ for number of pregnancies with GDM since index pregnancy

All other p-values > 0.05

Table 3.

Metabolic and cardiovascular biomarkers by baseline gestational diabetes mellitus (GDM) group

	Treated GDM (n=176)	Untreated GDM (n=158)	Non-GDM (n=308)	Unadjusted Mean difference (95% CI) Treated GDM*	Unadjusted Mean difference (95% CI) Untreated GDM*
IGI	2.42 ± 7.86	2.16 ± 6.27	1.86 ± 6.62	0.037 (−0.147 – 0.221)	−0.154 (−0.345 – 0.036)
1/HOMA	−0.90 ± 0.71	−0.86 ± 0.69	−0.71 ± 0.73	−0.188 (−0.321 – −0.056)	−0.149 (−0.286 – −0.118)
VEGF (pg/mL)	4.37 ± 0.75	4.33 ± 0.75	4.32 ± 0.76	−0.045 (−0.095 – 0.185)	0.003 (−0.142 – 0.148)
VCAM-1 (pg/mL)	13.70 ± 0.45	13.72 ± 0.43	13.78 ± 0.41	−0.085 (−0.164 – −0.006)	−0.067 (−0.149 – 0.014)
CD40L (pg/mL)	8.58 ± 0.56	8.63 ± 0.52	8.57 ± 0.61	0.007 (−0.099 – 0.113)	0.061 (−0.049 – 0.171)
GDF-15 (pg/mL)	6.26 ± 0.59	6.23 ± 0.47	6.23 ± 0.46	0.028 (−0.065 – 0.122)	−0.004 (−0.100 – 0.093)
ST-2 (pg/mL)	9.44 ± 0.46	9.47 ± 0.48	9.46 ± 0.46	−0.027 (−0.114 – 0.059)	0.004 (−0.085 – 0.093)

Data presented as mean +/− standard deviation or mean difference (95% confidence interval). All data was log-transformed except IGI for which Z-score transformations of ranked values were used.

Abbreviations: IGI, insulinogenic index; HOMA, homeostatic model assessment

*Referent = Non-GDM

Table 4.

Metabolic and cardiovascular biomarkers by baseline obesity

	Obese (n=301)	**Non-Obese (n=341)**	**Unadjusted Mean difference (95% CI) Obese***
IGI	2.04 ± 7.46	2.13 ± 6.37	0.084 (−0.070 – 0.238)
1/HOMA	−1.02 ± 0.63	−0.60 ± 0.73	−0.425 (−0.532 – −0.319)
VEGF (pg/mL)	4.35 ± 0.75	4.32 ± 0.75	0.029 (−0.088 – 0.146)
VCAM-1 (pg/mL)	13.71 ± 0.41	13.78 ± 0.43	−0.067 (−0.133 – −0.001)
CD40L (pg/mL)	8.61 ± 0.53	8.56 ± 0.60	0.043 (−0.046 – 0.132)
GDF-15 (pg/mL)	6.25 ± 0.45	6.23 ± 0.54	0.018 (−0.060 – 0.096)
ST-2 (pg/mL)	9.43 ± 0.47	9.48 ± 0.46	−0.046 (−0.118 – 0.026)

Data presented as mean +/− standard deviation or mean difference (95% confidence interval). All data was log-transformed except IGI, for which Z-score transformations of ranked values were used.

Abbreviations: IGI, insulinogenic index; HOMA, homeostatic model assessment

*Referent = Non-Obese