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Original Communication

Postpartum metabolic profiles in women with a recent history of gestational diabetes: variations by race

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ABSTRACT

Women with previous gestational diabetes mellitus (GDM) display a range of metabolic abnormalities. To characterize maternal metabolic profiles during the first year postpartum and to determine the relative contribution of race, women with recent GDM underwent a complete metabolic characterization 6-12 weeks after delivery (early) and 1 year (late) postpartum. From April 2009-April 2012, we prospectively evaluated 214 prior GDM women (pGDM; 168 Caucasian (W) and 46 African-American (NW)). Anthropometric measurements (weight, height, body mass index (BMI), waist circumference (WC), body fat distribution (waist/hip (W/H) and waist/height (WHt) ratio), blood pressure (BP) and blood specimens were obtained. Insulin and glucose concentrations at baseline, 30, 60, and 120 min during a 2-h 75-g oral glucose tolerance test (OGTT) were used to derive fasting and glucose-stimulated insulin sensitivity and insulin secretion indices. Fasting and mean blood glucose (FBG, MBG), total cholesterol (C), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TRG) were determined. The study cohort included 105 pGDM women (85 W, 20 NW) studied early and late postpartum. Seventy-nine pGDM women did not complete repeat testing and 30 women on medications for early postpartum dysglycemia were excluded from the analyses. At 1-year follow-up, dysglycemia was more prevalent in NW women with 50% having impaired glucose regulation compared to 25.9% of W women. NW pGDM women had lower insulin sensitivity and reduced β-cell function compared with W pGDM counterparts. Postpartum weight and WC gain, BP and MBG were also significantly greater in NW pGDM women. A less favorable lipid profile (higher LDL-C and TRG) was observed in W pGDM women. Weight gain, particularly increased central adiposity after delivery, and lower breastfeeding rates were strongly associated with deterioration of β-cell compensation for insulin resistance which is a key factor in the greater prevalence of glycemic impairment in NW pGDM women. The study was registered at http://www.clinicaltrials.gov (NCT00849849).

KEYWORDS: gestational diabetes, glucose metabolism, truncal adiposity, racial disparity

INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance that leads to hyperglycemia with onset or first recognition during pregnancy [1]. Whereas insulin action and secretion are both clearly impaired during pregnancies complicated by GDM, the extent and nature of the metabolic disturbances persisting after pregnancy remain unclear [2]. Although the majority of women with prior GDM (pGDM) return to normal glucose tolerance after delivery, they remain, as a group, at substantially increased risk of developing type

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2 diabetes (Type 2 DM) in later life suggesting that GDM is a transient manifestation of longstanding metabolic dysfunction [3]. The Diabetes Prevention Program showed that women who had a history of GDM had a 74% increased age-adjusted risk for diabetes compared to women who had no history of GDM [4]. In addition, up to one third of women with GDM have overt diabetes, impaired fasting glucose or impaired glucose tolerance identified immediately postpartum.

Race influences the prevalence of GDM, being higher in a non-white population, and racial/ethnic disparities exist in risk of diabetes after GDM [5]. Members of some ethnic groups are more prone to develop abdominal adiposity, and differences in fat distribution are considered a major contributor to the observed excessive prevalence of insulin resistance and diabetes among some racial and ethnic groups [6]. Racial and ethnic variations in the progression from GDM to permanent DM2 have also been described. In an analysis of pregnancies from southern California, GDM conferred greater risk for diabetes for non-Hispanic black women than for other racial/ethnic groups, even after consideration of BMI [5]. Because women of non-Hispanic black race/ethnicity have a similar prevalence of GDM to non-Hispanic white women, despite having a poorer diabetes risk factor profile (lower socioeconomic status, stronger family history for diabetes, greater BMI), it is possible that non-Hispanic black women who actually develop GDM may be at higher risk for diabetes.

Both insulin resistance and inadequate insulin secretion are indicated as the main causes of an increased risk of DM2 [2-6]. In the postpartum period, women with pregnancies complicated by GDM should be screened with an oral glucose tolerance test (OGTT) to identify type 2 DM as well as milder forms of dysglycemia. Indeed, it has emerged that in fact any degree of abnormal glucose tolerance detected on antepartum screening (i.e. not just GDM) predicts an increased future risk of pre-diabetes and diabetes, one that is proportional to the severity of dysglycemia observed in pregnancy [7]. Reports on carbohydrate metabolism indices following GDM have shown variable results, and we hypothesized that this variability reflected ethnic heterogeneity in different studies, small subject numbers, and different times between the index pregnancy and follow-up study. In order to characterize maternal metabolic profiles during the first year postpartum in pGDM women and to determine the racial impact, women with pGDM underwent a complete metabolic characterization early after delivery (6-12 weeks) and at 12 months postpartum. Also, we evaluated the perceived risk of diabetes and the readiness to engage in diabetes risk reduction behavior with respect to physical activity and achieving a healthy weight in this biracial cohort of women with a history of GDM.

MATERIAL AND METHODS

Participants

This was a hospital-based prospective cohort study that enrolled GDM subjects (n = 214) between April 2009-April 2011 who delivered at Woman's Hospital. Of the 214 women diagnosed with GDM (Carpenter-Coustan diagnostic criteria [8]) in the index pregnancy, 168 were Caucasian (white - W) and 46 were African-American (non-white - NW). Postpartum women with documented GDM were evaluated with a standardized clinical examination which included anthropometry and a 75 gram OGTT at 6-12 weeks after delivery (early postpartum). The study protocol was approved by the Woman's Hospital Foundation Institutional Review Board, and all participants provided written informed consent.

Participant examination

Patient information concerning breastfeeding, current medications and vitamins, first-degree family history of diabetes, smoking and alcohol use and demographic data were collected using standardized questionnaires. Race/ethnicity was self-identified by participants. Anthropometric measurements and blood specimens were obtained by trained personnel using standardized protocols at the baseline and follow-up examinations. Absolute body weight, height, waist and hip circumference, body fat distribution (waist/hip (WHR) and waist/height ratio (WHtR)) and blood pressure (BP) were determined. Body weight was measured to the nearest 0.1 kg using a calibrated digital scale with participants in light clothing and no shoes. Height was measured to the nearest 1.0 cm. Height and weight measurements were used to calculate body mass index (BMI) equal to weight [kg]/height^2 [meters]. BMI values of 18.5-24.9 kg/m^2 were considered to be normal,

25.1-30 kg/m^2 overweight, and >30 kg/m^2 obese. Waist circumference (WC) was measured at the narrowest level midway between the lowest ribs and the iliac crest and hip circumference was measured at the widest level over the buttocks while the subjects were standing and breathing normally. The WHR and WHtR were calculated and used to estimate abdominal adiposity. A WC >35 inches, WHR >0.72 and WHtR >0.5 were considered to be elevated indicating increased cardiometabolic risk [9].

An OGTT was administered to all participants at Woman's Hospital Outpatient Pathology Laboratory at 6-12 weeks postpartum. The test was performed in the morning (starting at 7:00-10:00 AM) after a 12-hour overnight fast. After the collection of an antecubital venous baseline blood sample, a 75-g oral glucose load was administered; additional blood samples were drawn 30, 60, and 120 min later for analysis of glucose and insulin levels. Blood specimens were also collected in the fasting state for measurement of lipids (cholesterol, HDL and LDL cholesterol, triglycerides). Two questionnaires were administered at the early postpartum visit. The first questionnaire was to collect information about perceived diabetes risk which was assessed using a six-point Likert scale, with responses ranging from strongly agree to strongly disagree [10]. Stage of change was measured using validated questionnaires adapted from Marcus *et al.* [11] in which participants reported stage of change for physical activity and current weight loss behavior.

Participants were asked to return approximately 1 year after delivery for a late postpartum metabolic reassessment that included anthropometric measurements and evaluation of glucose tolerance by a 75-g OGTT. The blood specimens were collected in the fasting state (time = 0), and 30, 60 and 120 minutes after the 75-g oral glucose load. One hundred and thirty five pGDM women (113 W; 22 NW) completed the follow-up stage of the study, 79 pGDM (55 W, 24 NW) did not complete late postpartum follow-up. To minimize confounding factors, only women who received no regular postpartum medical treatment for glucose tolerance were included in the final analyses. Thirty participants (28 W, 2 NW) on medical therapy for prediabetes diagnosed early postpartum were excluded from analyses.

Laboratory measures

Blood samples were collected from each participant in different storage media (EDTA and plain tubes) and were sent for processing within 10 minutes of collection or stored on ice for processing within 60 minutes in the hospital clinical biochemistry laboratory. Glucose concentrations were measured in all samples before and after oral glucose challenge by the glucose oxidase method using the Vitros Chemistry System (Ortho Vitros 5600 System; Ortho-Clinical Diagnostics, Raritan, NJ). Baseline and post-treatment serum levels of insulin were analyzed by paramagnetic particle chemiluminescent immunoassay using a Beckman Coulter Access 2 Analyzer (Beckman Coulter, Brea, CA). Levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TRG) were also determined from the initial fasting sample using an automated clinical chemistry analyzer (Ortho Vitros 5600 Chemistry System). The intra- and interassay coefficients of variation were not exceeding 8.6% at low and high values for all assays performed.

Physiologic indices

Postpartum glucose tolerance status was assessed according the American Diabetes Association diagnostic criteria [12]. Using the baseline value, glucose values less than 100 mg/dL (5.6 mmol/L) were classified as normal, values between 100 and 125 mg/dL (5.6-6.9 mmol/L) classified as impaired fasting glucose (IFG), and values of 126 mg/dL (7 mmol/L) or greater classified as diabetes. A 2-hr postload glucose value <140 mg/dL (<7.8 mmol/L) defined normal glucose tolerance; 2-h glucose ≥200 mg/dl (>11.1 mmol/L) was the criterion for diabetes whereas impaired glucose tolerance [IGT] was defined as a 2-h glucose concentration ≥140 and <200 mg/dl (7.8-11.1 mmol/L) after a 75-g glucose load in the presence of a fasting glucose concentration <100 mg/dl. Combined IFG/IGT was defined by fasting glucose between 100 and 125 mg/dL (5.6-6.9 mmol/L) and 2-h postload glucose concentration ≥140 and <200 mg/dl (7.8-11.1 mmol/L). Postpartum dysglycemia collectively refers to prediabetes (IFG, IGT and combined IFG/IGT) and type 2 DM.

Fasting blood glucose (FBG) and mean blood glucose (MBG) concentrations were calculated in

milligrams per dl from glucose levels obtained during the OGTT. Hyperinsulinemia was considered when fasting levels were >10 mU/l and >40 mU/l, 2 h post-load. Dyslipidemia was defined as the presence of at least one of the mentioned lipid abnormalities-total cholesterol >200, HDL <50, LDL >130, TRG greater than 175 and/or TRG/HDL ratio greater than 3.0.

Indexes of insulin sensitivity and secretion using the glucose and insulin concentrations obtained in the fasting state and during the two-hour OGTT were computed by several measures previously validated in women. Fasting insulin sensitivity was estimated by homeostasis model assessment of insulin resistance (HOMA-IR) according to the report of Matthews *et al.* [13]. The glucose-stimulated insulin sensitivity index [SI_{OGTT}] was derived from OGTT using the Matsuda whole-body composite model [14], which has been shown to be strongly correlated with the hyperinsulinemic-euglycemic clamp. The fasting component reflects hepatic insulin sensitivity, whereas the mean of the dynamic data primarily represents skeletal muscle insulin sensitivity. This partitioning concept has been validated using glucose clamp studies. An estimation of acute pancreatic β-cell response to glucose was calculated using the insulinogenic index (IGI $\Delta I30/\Delta G30$) [15] corrected with the relative level of insulin resistance (IGI/HOMA-IR) [16]. The corresponding oral disposition index (DI_{OGTT} = $\Delta I30/\Delta G30$ multiplied by the SI_{OGTT}) was calculated as the product of insulin sensitivity (SI_{OGTT}) and acute β-cell response [IGI] based on the existence of the predicted hyperbolic relationship between these two measures [17]. Because this index accounts for the glucose levels, it quantifies β-cell sensitivity to glucose, not absolute insulin secretion.

Statistical design

Statistical analyses were performed using the SPSS software package for Windows (version 15.1, SPSS, Chicago, IL). The normality of all variables was checked using the Kolmogorov-Smirov test. For comparisons of continuous measures, analyses of variance were performed using one-way and repeated-measures model analysis of variance (ANOVAs) as appropriate. Adjustments for multiple testing were performed using Bonferroni correction. The Kruskal-Wallis test was used to compare differences in frequency data between groups. The p value for statistical significance was set at <0.05. Results are presented as mean +/- standard error of the mean (SEM) and in percentages unless otherwise indicated.

The responses for perception of diabetes risk questions were categorized as disagree (1 & 2), neither agree nor disagree (3 & 4), and agree (5 & 6). Respondents to state of change were divided into pre-action (pre-contemplation, contemplation and preparation stages) and action (action and maintenance stages) groups for comparative analyses [11]. Each completed questionnaire was coded, entered into a database and analyzed. Statistical tests (χ squared, Fisher exact probability test, frequencies and cross tabulations) were conducted to test for differences in responses between the groups.

RESULTS AND DISCUSSION

The obstetric, clinical and cardiometabolic characteristics of the 105 pGDM study participants (85 W, 20 NW) stratified by race are presented in Table 1. Obesity was highly prevalent with 80 (76.4%) pGDM women having a prepregnancy BMI >25. Obstetrical characteristics of the participants were not racially disparate (Table 1). NW pGDM women were significantly heavier ($p < 0.007$) with increased abdominal adiposity (larger WC [$p < 0.03$] and higher WHR [$p < 0.01$] and WHtR [$p < 0.004$]) than their W p-GDM counterparts (Table 1). Abnormal lipid profiles were more prevalent in W pGDM women (65%) early postpartum compared with NW pGDM women (50%). W p-GDM women had significantly higher LDL-CHOL levels ($p < 0.001$) whereas NW p-GDM women had significantly increased systolic ($p < 0.012$) and diastolic ($p < 0.001$) BP and insulin resistance ($p < 0.023$) (Table 1). No difference in β-cell compensatory ability following glucose stimulation ($DI_{OGTT)}$ was observed between the two groups (Table 1).

The clinical and metabolic characteristics of pGDM study participants at 1 year postpartum are shown in Table 2. Of this pGDM population that had normal glucose tolerance early postpartum, 30.5% (32/105) had developed dysglycemia, with 3.8% (4/105) having converted to type 2 DM

Table 1. Clinical, anthropometric and cardiometabolic measures at 6-12 weeks post-partum stratified by race.

Variable	White (n = 85)	Non-White (n = 20)	p-value
Age (years)	31 (0.5)	30.3 (0.9)	0.63
Gravida	2.3 (0.15)	3.2 (0.41)	0.03
Parity	2.0 (0.12)	2.3 (0.15)	0.11
Recurrence of GDM (%)	59 (69)	17 (84)	0.23
C-section rate (%)	40 (47)	10 (50)	0.77
LGA baby (%)	20 (24)	4 (21)	0.81
BMI (kg/m^2)	29.6 (0.8)	34.2 (1.4)	0.007
WC (inches)	34.8 (0.6)	0.38.2 (1.1)	0.03
WH ratio	0.78 (0.006)	0.82 (0.009)	0.011
WHt ratio	0.54 (0.009)	0.60 (0.016)	0.004
Systolic BP (mmHg)	117.7 (1.5)	126.8 (1.8)	0.012
Diastolic BP (mmHg)	70.6 (0.71)	78 (1.6)	0.001
HOMA-IR	2.2(0.26)	2.8 (0.35)	0.25
SI_{OGTT}	8.03 (0.65)	5.03 (0.74)	0.023
IGI/IR	0.76(0.11)	0.85 (0.18)	0.989
DI index	6.4 (1.02)	6.8 (1.85)	0.868
LDL-CHOL (mg/dL)	132.3 (3.6)	102.8 (6.5)	0.001
TRG (mg/dL)	148 (8.6)	121.5 (15.8)	0.184
TG/HDL-CHOL ratio	2.8 (0.22)	2.5 (0.39)	0.486

Data are mean (+/- S.E.M) or n (%).

late postpartum. The prevalence of dysglycemia was significantly higher in NW pGDM women at the 1-year evaluation. Fifty-percent (10/20) of NW pGDM women had dysglycemia with 10% (2/20) having type 2 DM compared to 26% (22/85) dysglycemia and 2.4% (2/85) type 2 DM found in W pGDM participants ($p < 0.036$; Table 2). Fasting blood glucose levels were similar in the two groups, whereas mean OGTT blood glucose concentrations were significantly higher in the NW pGDM group than in the W pGDM group ($p < 0.03$). NW pGDM women showed significantly greater insulin resistance (HOMA, SI_{OGTT}), inadequate insulin response to glucose (IGI/HOMA-IR) and elevated systolic and diastolic BP but significantly lower fasting TRG and LDL-cholesterol levels as compared to their W pGDM counterparts (Table 2). The DI_{OGTT} was significantly reduced ($p < 0.003$) in the NW pGDM group suggesting greater β-cell dysfunction following glucose stimulation. We did not perform analyses that adjusted the DI_{OGTT} for measures of adiposity since the DI_{OGTT} represents a measure of β-cell function that already takes account of prevailing insulin sensitivity. W pGDM women were more likely to breastfeed ($p < 0.008$) than NW pGDM women (Table 2). Age, HDL-cholesterol (CHOL) and TRG/HDL-CHOL ratio were similar in the two groups (Table 2).

At one year, mean BMI had increased in NW women with pGDM while a mean decrease in BMI from early to late postpartum was seen in W pGDM women ($p \leq 0.018$; Table 1). Figure 1 illustrates the change in mean BMI for W (dark grey) and NW (light grey) pGDM women over time from prepregnancy, to early postpartum to late post-partum screening. While all pGDM women were heavier at the early postpartum visit compared to their prepregnancy weight, NW pGDM gained weight whereas W pGDM lost weight from early postpartum testing to the late postpartum evaluation. Late postpartum NW pGDM women had a significant gain in WC

Table 2. Anthropometric and cardiometabolic measures at one year post-partum stratified by race.

Variable	White	Non-White	p-value
Age (years)	31.3 (0.6)	31.6 (1.3)	0.82
Breastfeed (%)	45 (52.9%)	4 (20%)	0.008
Dysglycemia (%)	22 (25.9%)	10 (50%)	0.036
ΔBMI (kg/m^2)	-0.37 (0.26)	+1.0 (0.54)	0.018
ΔWC (inches)	-0.3 (0.2)	+1.0 (0.57)	0.023
ΔWH ratio	0.006 (0.005)	0.018 (0.009)	0.28
ΔWHt ratio	-0.005 (0.004)	0.16 (0.009)	0.044
Systolic BP (mmHg)	118.7 (1.1)	130 (4.1)	0.001
Diastolic BP (mmHg)	71.4 (0.8)	79.2 (2.4)	0.001
FBG (mg/dL)	85.6 (1.0)	89.4 (2.3)	0.12
MBG (mg/dL)	111.9 (1.9)	122 (4.8)	0.03
HOMA-IR	2.0 (0.19)	5.2 (1.6)	0.001
SI_{OGTT}	7.6 (0.6)	3.8 (0.4)	0.002
IGI/IR	0.77 (0.11)	0.4 (0.8)	0.014
DI index	8.4 (2.1)	1.9 (0.5)	0.003
LDL-C (mg/dL)	107.9 (3.5)	95 (5.6)	0.045
TRG (mg/dL)	133 (8.4)	103 (10.2)	0.028
TG/HDL-C	2.7 (0.25)	2.2 (0.27)	0.38

Data are mean (+/- S.E.M) or n (%).

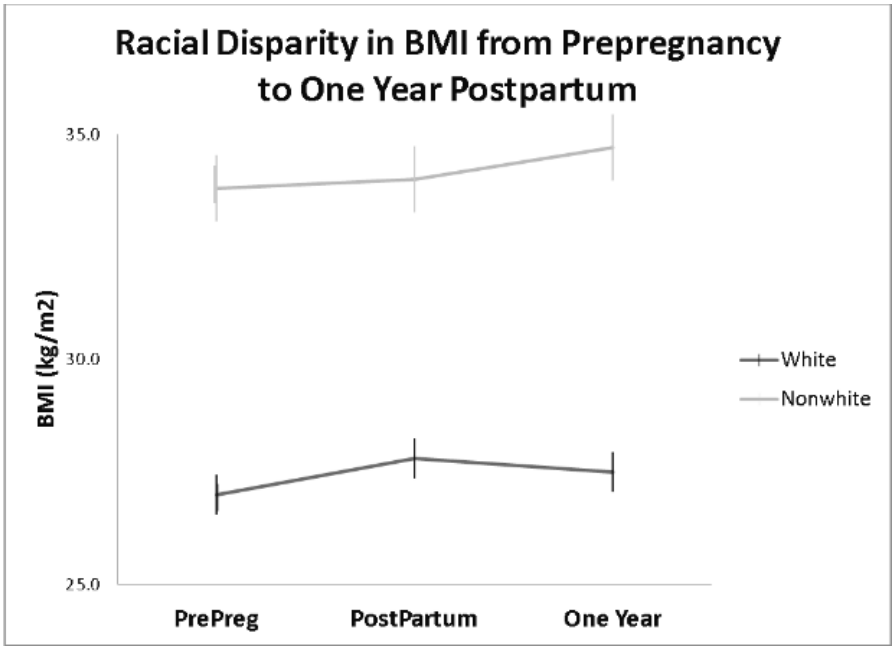

Figure 1. The change in mean body mass index (BMI) +/- S.E.M. in W (dark line) and NW (light line) women with GDM over time from prepregnancy, to early postpartum screening and at one year post-partum (85 W; 20 NW subjects). While all prior GDM women were heavier at the initial postpartum visit compared to prepregnancy weight, NW pGDM gained weight whereas W pGDM lost weight at the one year postpartum evaluation ($p \leq 0.048$).

compared to a loss seen in their W pGDM counterparts ($p < 0.023$; Table 2). Change in WHtR in W and NW pGDM women at the time of early postpartum screening and late post-partum is shown in Figure 2. The WHtR, a simple predictor of intrabdominal fat, significantly increased in NW pGDM women at 1 year postpartum whereas a decrease was seen in W PGDM women ($p < 0.045$). No significant differences in WHR changes were observed between the pGDM groups (Table 2).

The responses of study participants relating to risk of developing diabetes are summarized in Table 3A. The majority of both W and NW pGDM women agreed healthy lifestyle choices, eating a healthy diet, maintaining a healthy weight and doing regular exercise, were important for good health. Greater than 75% of respondents disagreed with the statements in the perceived risk questionnaire of not being motivated about their health or on feeling that they would get diabetes no matter what they did (Table 3A). NW women were significantly more confident than W pGDM women that they could prevent diabetes (86% vs. 67%, $p < 0.002$) and that reminders by a diabetes center or doctor would help them prevent Type 2 DM (86% vs. 64%, $p < 0.002$). Stage of change questionnaire results, shown in Table 3B, revealed no differences between W and NW pGDM participants in terms of physical exercise with greater than 70% participating in no physical activity at the early postpartum visit. In contrast, a significant difference was found for weight loss behavior with 37% of W pGDM women participating in active weight loss compared with only 25% of NW pGDM women ($p < 0.04$) in the early postpartum period (Table 3B).

Loss to follow-up

In this investigation, metabolic testing was repeated at 1 year postpartum on non-pregnant women meeting non-diabetic condition (according to the American Diabetes Association [12]). Eight subjects (3.8%) having a diagnosis of Type 2 DM and 14 subjects (6.6%) pregnant before the 1-year assessment were not retested at 1 year; 57 pGDM women did not return (26.6%). To exclude the secondary influence of insulin sensitivity and β cell function

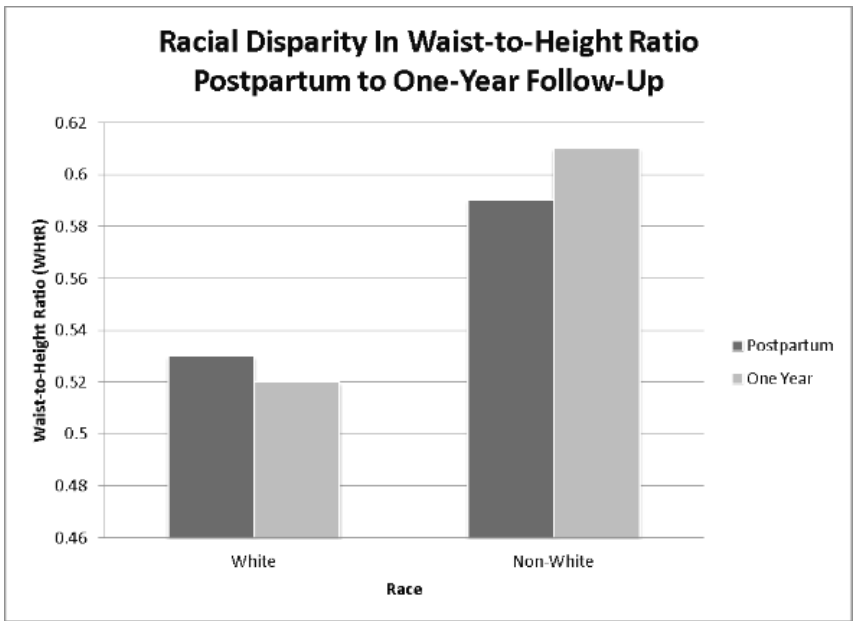

Figure 2. Mean waist to height ratio (WHtR) +/- S.E.M. fluctuations in W (n = 85) and NW (n = 20) prior GDM women at the time of early postpartum screening (dark bars) and at one year post-partum visit (light bars). The WHtR, a simple predictor of intrabdominal fat, was significantly increased in NW pGDM women at 1 year postpartum whereas a decrease was seen in W PGDM women ($p \leq 0.04$).

Table 3A. Perception of risk of developing diabetes.

White	Agree (%)	Neither (%)	Disagree (%)
Eating a healthy diet is important to my health	100	0	0
Maintaining a healthy weight is important to my health	100	0	0
Regular exercise is important to my health	94	5	1
It is important for me to prevent diabetes	95	3	2
Regularly being reminded to have a blood glucose test by diabetes center or doctor will help prevent it	65	30	5
I am confident I can prevent diabetes	67	27	6
I do not feel motivated about my future health	12	10	78
I feel I will get diabetes no matter what I do	5	24	71
Non-White	Agree (%)	Neither (%)	Disagree (%)
Eating a healthy diet is important to my health	100	0	0
Maintaining a healthy weight is important to my health	100	0	0
Regular exercise is important to my health	100	0	0
It is important for me to prevent diabetes	96	4	0
Regularly being reminded to have a blood glucose test by diabetes center or doctor will help prevent it	86	12	2
I am confident I can prevent diabetes	86	14	0
I do not feel motivated about my future health	12	6	82
I feel I will get diabetes no matter what I do	4	21	70

Table 3B. Stage of change.

Exercise

State at Baseline	White	Non-White
Pre-Action (%)	72	73
Action (%)	28	27

Weight loss

State at Baseline	White	Non-White
Pre-Action (%)	63	75
Action (%)	37	25

from abnormal glucose tolerance, only those women who were known to be glucose tolerant at the early postpartum screening were included for comparison analyses for assessment of β cell function and insulin sensitivity late postpartum. Of the 135 pGDM women (63% of total study population) evaluated early and late postpartum, 30 participants (28 W, 2 NW) treated with medical therapy for prediabetes diagnosed early postpartum were not included in the analyses.

CONCLUSIONS

We studied a group of postpartum women with a history of GDM, a population known to be at increased risk of developing Type 2 DM in later life [2-7]. In order to avoid the confounding effects of hyperglycemia (and/or its treatment) on the intermediate metabolic traits, we restricted our analysis to women with normal glucose homeostasis early postpartum, focusing therefore on the subset of women with previous GDM likely to have the least marked metabolic defects. We found that the women with a history of GDM, even when they have normal fasting glucose, display metabolic abnormalities, including reduced insulin sensitivity as well as impaired pancreatic β-cell function. Other studies examining insulin action and secretion in normoglycemic women with a history of GDM using varying methodologies have shown a range of metabolic defects which are influenced by race [5, 6, 18, 19]. Xiang *et al.* [19] in a large study, identified defects in both insulin action and secretion in 116 Latino women with previous GDM compared with 25 control women. We observed racial

differences in basal and post-stimulation glucose homeostatic regulation over the spectrum of glucose tolerance with NW pGDM women having a higher risk of converting to dysglycemia at one year postpartum. Also, although the insulinogenic index was increased in NW pGDM women, indicating increased β-cell function in the basal state, the OGTT-derived disposition index showed reduced β-cell function following glucose stimulation, suggesting impaired compensatory capacity of the β-cell.

Postpartum weight retention is a significant contributor to overweight and obesity, and was predictive for the persistence of glucose intolerance in the first year postpartum regardless of ethnicity. The majority of pGDM NW women manifested postpartum weight gain, characterized by abdominal adiposity, which may be a key factor in the greater prevalence of glycemic impairment in this racial group. Adiposity has been linked to disease progression before and after the development of IGT [20]. Although the exact mechanisms by which weight gain and obesity promote incident Type 2 diabetes are not understood fully; a combination of adiposity-generated insulin resistance and deterioration in pancreatic β-cell function are likely to blame. The significant association between declining β-cell compensation and weight gain confirmed the observations made previously by Weyer *et al.* [21] in Pima Indians and by Kriketos *et al.* [22] in women with a family history of Type 2 DM. In Pima Indians, weight gain was associated with progression from normal glucose tolerance to IGT and from IGT to diabetes [21]. In the Diabetes Prevention Program, central adiposity predicted future development of Type 2 DM in overweight/obese individuals with IGT [23]. Moreover, a lifestyle intervention resulting in weight loss was effective in both decreasing the rate of conversion to diabetes by 58% and reverting IGT to normal in 40% of participants. Our findings highlight the importance of reducing body fat and its detrimental metabolic effects to preserve pancreatic β-cell function and prevent the progression to diabetes in high-risk prior GDM individuals.

Prediabetes/diabetes in the first year postpartum appears to be reduced by breastfeeding. Lactation, even for a short duration, appears to have beneficial effects on glucose metabolism and insulin sensitivity and offers a practical and low-cost intervention to reduce the risk of subsequent diabetes in women with recent GDM. Two large studies, one from Denmark [24] and one among racially diverse women in the United States [25], show a positive effect of breastfeeding on long-term post-partum weight loss compared with formula feeding, with stronger effects with more intensive and longer duration of breastfeeding. White pGDM women were more likely to have breastfed their babies compared with their NW pGDM counterparts. Several factors have been shown to impact breastfeeding such as family/spouse support, return to work or school, and cultural factors [26]. Given that exclusive breastfeeding can lead to reduced weight retention in the post-partum period, post GDM women may benefit more from exclusive breastfeeding.

There is limited literature exploring lifestyle choices in women with a history of GDM. The majority of the women expressed a high level of motivation, optimism and confidence to prevent diabetes along with a high awareness of the importance of regular physical activity, healthy weight and healthy diet. However, previous research has indicated that women with a history of GDM, although concerned about their health and aware of their risk of developing diabetes, do not necessarily engage in risk reduction behavior [27]. Competing responsibilities can alter sleeping habits, work schedules, eating patterns, exercise regularity and time allocation that challenge even the most committed mother of young children [27, 28]. In the present study, the majority of pGDM NW women were still in the pre-action or preparation stage for activity and weight loss (planning to do more physical activity and losing weight in the next months). Although they were concerned about developing overt diabetes, only a few had changed their lifestyle and/or lost weight after pregnancy. The women in this study, while motivated, were not ready to adopt healthy lifestyle behaviors. Clearly, strategies to assist this population to overcome barriers to achieve lifestyle changes and stimulate physical activity to effect maintenance of lower weight in the postnatal period are needed.

There are some limitations of our study that should be considered. The size of the analyzed population

was small, a substantial number of patients were lost to follow-up and the number of NW participants was much less compared to W participants. It remains to be seen whether these differences would be even greater with a larger population sample. Second, surrogate measures were used to estimate insulin sensitivity and secretion. While glucose clamp techniques are considered to be the gold standard to assess insulin sensitivity and beta-cell function, these methods are not practical in clinical studies which need to rely on surrogates; therefore, for the patients in the present study, we used measures derived from the OGTT. In general, surrogate measures of IR that incorporate both fasting and postload values are stronger predictors of future diabetes than fasting levels alone [29] although beyond that the choice is less clear. Of the surrogates at our disposal, the Matsuda index provided the most complete explanation for ethnic differences in risk. Although not routinely obtained, assessment of insulin secretion, both during and after pregnancy, provides the strongest independent predictors of diabetes in the mother [30].

In conclusion, women with previous GDM provide an opportunity to study diabetes in evolution. Weight gain, particularly increased central adiposity after delivery, was strongly associated with deterioration of β-cell compensation for insulin resistance. We found that WC and WHtR were significantly better predictors than absolute weight or WHR. Waist size and waist to height ratio have less measurement error compared to waist-to-hip ratio and are more reliable measures of central adiposity. Taken together, our findings support increased abdominal fat as the strongest factor associated with declining B-cell compensation for insulin resistance in pGDM women at high risk for Type 2 DM.

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CONFLICT OF INTEREST STATEMENT

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