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Post-partum weight loss and glucose metabolism in women with gestational diabetes: the DEBI Study

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Abstract

Aims—Women with gestational diabetes are at high risk for developing diabetes; post-partum weight loss may reduce the risk of diabetes. We evaluated the association of post-partum weight change with changes in glucose, insulin and homeostasis model assessment levels in a subsample (n = 72) of participants from Diet Exercise and Breastfeeding Intervention (DEBI), a randomized pilot trial of lifestyle intervention for women with gestational diabetes.

Methods—Glucose and insulin were measured fasting and 2 h after an oral glucose tolerance test at 6 weeks and 12 months post-partum. Women were categorized by weight change (lost > 2 kg vs. maintained/gained) between 6 weeks and 12 months post-partum.

Results—Compared with women who maintained or gained weight, women who lost > 2 kg experienced significantly lower increases in fasting glucose [age-adjusted means: 0.1 mmol/l (95% CI −0.03 to 0.3) vs. 0.4 mmol/l (95% CI 0.3–0.6); P < 0.01] and 2-h insulin [10.0 pmol/l (95% CI −56.9 to 76.9) vs. 181.2 pmol/l (95% CI 108.3–506.9); P < 0.01] and a significant reduction in 2-h glucose [−0.9 mmol/l (95% CI −1.4 to −0.3) vs. 0.3 mmol/l (95% CI −0.3 to 0.9); P < 0.01]. In multiple linear regression models adjusted for age, Hispanic ethnicity, medication use, meeting the Institute of Medicine's recommendations for gestational weight gain, breastfeeding and randomized group, a 1-kg increase in weight was significantly associated with increases in fasting and 2-h glucose (P < 0.05), but was not associated with insulin or homeostasis model assessment of insulin resistance.

Conclusions—In women with gestational diabetes, modest post-partum weight loss may be associated with improvements in glucose metabolism.

Introduction

The retention of pregnancy weight is associated with an increased risk of long-term overweight [1], as pregnancy weight retention at 1 year post-partum has been shown to

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Competing interests
None declared.

predict being overweight 15 years later [2]. Women with gestational diabetes mellitus, defined as carbohydrate intolerance with first onset or recognition in pregnancy [3], also face an increased risk of obesity-related co-morbidities, particularly diabetes. The prevalence of gestational diabetes in the USA is 4–7% [4,5], with 35–100% increases in prevalence reported over the last several decades [5–8]. Women with gestational diabetes are seven times more likely to develop diabetes later in life compared with women with normoglycaemic pregnancies [9]; thus the retention of pregnancy weight is of particular concern in this population.

Post-partum weight loss may reduce the risk of diabetes in women with a pregnancy affected by gestational diabetes. O'Sullivan [10] reported that, after 23 years of follow-up on women with a history of gestational diabetes, diabetes was present in 61% of those who were obese prior to pregnancy, 42% of those who had gained weight since pregnancy and only 28% of those who were not obese prior to pregnancy or had since lost weight. Peters *et al*. [11] revealed that, among 666 Latino women with a recent history of gestational diabetes, post-partum weight gain of 4.5 kg was independently associated with a twofold increase in the risk of developing diabetes.

Our randomized controlled Diet Exercise and Breastfeeding Intervention (DEBI) pilot trial demonstrated that a lifestyle intervention for women with gestational diabetes that started during pregnancy and continued post-partum was feasible and may be effective in preventing pregnancy weight retention and promoting post-partum weight loss [12]. Yet there is a paucity of data on the association between post-partum weight change and glucose metabolism and insulin sensitivity in women with gestational diabetes. This study aims to investigate the association of post-partum weight change, particularly post-partum weight loss, with changes in glucose and insulin levels measured fasting and 2 h after a standard 75-g oral glucose tolerance test, as well as with change in homeostasis model assessment (HOMA) levels, in the first year post-partum among women with gestational diabetes.

Methods

The DEBI randomized pilot trial evaluating the feasibility of a lifestyle intervention for women with gestational diabetes has been described in detail elsewhere [12]. Briefly, trial participants (n = 197) were women receiving care at Kaiser Permanente Northern California (KPNC) between October 2005 and May 2008 who had been diagnosed with gestational diabetes in accordance with the American College of Obstetricians and Gynecologists (ACOG) criteria [13]. Women were randomly assigned to a lifestyle intervention group or usual care (control) group upon completion of the first study clinic visit, which occurred shortly after the diagnosis of gestational diabetes (mean gestational age at enrolment 31.4 weeks, SD 5.9).

The DEBI lifestyle intervention, which was adapted from the Diabetes Prevention Program curriculum, started soon after the diagnosis of gestational diabetes and continued post-partum. The goal of the post-partum intervention for women whose pregravid BMI was normal (< 25.0 kg/m^2) was to reach pre-pregnancy weight by 12 months post-partum, and for women whose pregravid BMI was overweight or obese (≥ 25.0 kg/m^2), to lose an

additional 5% of their pre-pregnancy weight by 12 months post-partum. The intervention encouraged women to achieve their weight management goals through healthy eating (e.g. reducing dietary fat intake), physical activity and breastfeeding. Study dieticians delivered a maximum of three antenatal sessions and 16 post-partum sessions, primarily by telephone. Study lactation consultants also offered telephone counselling to encourage women to breastfeed exclusively for 6 months.

Participants were asked to attend four clinic visits for data collection: (1) during pregnancy and (2) at 6 weeks, (3) 7 months and (4) 12 months post-partum. Data were collected by trained research assistants who were unaware of the participants' group assignment. Weight was measured at each visit with a Tanita WB-110 digital electronic scale (XXXX, XXX, XXXX); height was measured at baseline using a standard stadiometer. Self-reported pregravid weight and measured height were used to calculate pregravid BMI (kg/m^2). Total gestational weight gain was calculated as the difference between the last weight measured during pregnancy (obtained from the medical record) and self-reported pregravid weight. In accordance with the Institute of Medicine's recommendations for appropriate gestational weight gain that were in place at that time [14], total gestational weight gain was categorized as exceeding the Institute of Medicine's recommendations (vs. not exceeding the recommendations).

Information on the use of diabetes medications during pregnancy was obtained from the medical records. Data on partial or exclusive breastfeeding were collected at 6 weeks and 7 months post-partum with the question, 'Are you now feeding your baby any breast milk?' Information on participation in moderate- and vigorous-intensity physical activity during the previous week [15] was collected at the clinic visit at 7 months post-partum.

Beginning in May 2007, an ancillary study was initiated and trial participants were asked to complete a standard 75-g oral glucose tolerance test, following an 8-h fast, at 6 weeks and at 12 months post-partum. Plasma glucose values were measured at the Kaiser Permanente Northern California clinical laboratory using the hexokinase method; this laboratory participates in the College of American Pathologists accreditation and monitoring programme. An additional 4 ml of blood was taken at both the fasting and 2-h blood draws of the oral glucose tolerance test, and insulin levels were measured by a two-site immuno-enzymometric assay performed using a Tosoh 600 II auto-analyser (XXXXX, XXX, XXXX) at the Northwest Lipid Research Laboratories, University of Washington, Seattle, Washington. Insulin present in the samples was bound with a monoclonal antibody immobilized on a magnetic solid-phase and an enzyme-labelled monoclonal antibody. The magnetic beads were washed to remove unbound enzyme-labelled monoclonal antibody and then incubated with a fluorogenic substrate, 4-methylumbelliferyl phosphate. The amount of enzyme-labelled monoclonal antibody that binds to the beads is directly proportional to the immuno-reactive insulin concentration in the sample. A standard was constructed using a calibrator of known concentration and participants' insulin concentrations were calculated using this curve.

Measures of fasting glucose and insulin were also used to approximate insulin resistance using the homeostasis model assessment (HOMA-IR) equation described by Matthews *et al*. [16].

Statistical analyses

We evaluated differences in glucose, insulin and HOMA by post-partum weight change group [lost weight (> 2 kg) vs. maintained or gained weight between 6 weeks and 12 months post-partum] using Fisher's exact test, the χ^2-test, Student's *t*-test or the Wilcoxon rank sum test. We then compared the age-adjusted means of glucose, insulin and HOMA at 6 weeks and 12 months post-partum, as well as the age-adjusted change in glucose, insulin and HOMA over this period (12-month levels minus 6-week levels), by post-partum weight change group with analysis of variance (ANOVA). Comparisons of log-transformed, age-adjusted mean levels of glucose, insulin and HOMA at 6 weeks and 12 months post-partum, as well as the change in the log-transformed levels, lead to comparable inference; therefore, non-transformed estimates are presented for ease of interpretation.

Multiple linear regression analyses modelled the independent effects of post-partum weight change (1 kg, continuous) on post-partum change in glucose, insulin and HOMA. Variables were as considered potential confounders if they were associated with post-partum weight change (continuous) and the biomarker outcomes. Potential confounders were explored through a change-in-estimate strategy. Potential confounders that altered the age-adjusted coefficient estimates for post-partum weight loss by greater than 10% were retained for the fully adjusted regression models; these included: age, Hispanic race–ethnicity (vs. non-Hispanic race– ethnicity), any medication use in pregnancy (vs. none), exceeded the Institute of Medicine's recommendations for gestational weight gain (vs. not), breastfeeding at 7 months post-partum (vs. not) and randomized group (lifestyle intervention vs. usual care).

Results

From May 2007 to the end of the trial in May 2008, 116 women were enrolled. Of these 116 women, 72 had glucose or insulin measurements available for analyses (62%). Women without glucose or insulin measurements did not differ from those with these data with regard to randomized group assignment, maternal age, race–ethnicity, parity, BMI at 6 weeks post-partum and breastfeeding at 7 months post-partum. Among the 72 women with post-partum glucose or insulin data, 38 women (53%) lost > 2 kg, 16 women (22%) gained > 2 kg and 18 women (25%) maintained their weight (± 2 kg) between 6 weeks and 12 months post-partum.

Characteristics of the analytic cohort, by post-partum weight change group, are presented in Table 1. Compared with women who lost > 2 kg in the post-partum period, those who gained or maintained weight were significantly more likely to be of Hispanic ethnicity and to have attained lower levels of education. Women who lost weight and those who maintained or gained weight did not differ significantly with regard to randomized group, age at delivery, parity, BMI at 6 weeks post-partum or breastfeeding at 7 months post-partum (Table 1). The groups also did not differ in the proportion exceeding the Institute of Medicine's recommendations for total gestational weight gain (Table 1).

Table 2 presents age-adjusted mean glucose, insulin and HOMA levels at 6 weeks and 12 months post-partum, as well as the change in glucose, insulin and HOMA levels over the same period, by post-partum weight change group. At 6 weeks post-partum, women who would go on to lose weight had significantly lower fasting insulin and HOMA values compared with women who maintained or gained weight. At 12 months post-partum, women who had lost weight had significantly lower fasting glucose, fasting insulin, 2-h insulin and HOMA values compared with those who maintained or gained weight. No difference in 2-h glucose levels by post-partum weight change group were observed at 6 weeks or 12 months post-partum. Fasting glucose levels, fasting and 2-h insulin levels, and HOMA increased from 6 weeks to 12 months post-partum in both women who lost > 2 kg and those who did not (Table 2). As compared with women who maintained or gained weight, women who lost > 2 kg experienced significantly lower increases in fasting glucose and 2-h insulin, as well as a significant reduction in 2-h glucose (all $P < 0.01$). The mean change in fasting insulin and HOMA did not significantly differ between weight change groups.

The results of multiple linear regression analyses, with sequential adjustment for age, Hispanic ethnicity, medication use during pregnancy, exceeding the Institute of Medicine's recommendations for gestational weight gain, breastfeeding at 7 months post-partum and randomized group are presented in Table 3. In fully adjusted analyses (i.e. model 6), a 1-kg increase in weight between 6 weeks and 12 months post-partum was significantly associated with a 0.028-mmol/l increase in fasting glucose (SE 0.013; $P = 0.03$) and a 0.14-mmol/l increase in 2-h glucose (SE 0.046; $P = 0.01$). In the fully adjusted models, there was the suggestion of an association between a 1-kg increase in weight and a 12.51-pmol/l (SE 6.77; $P = 0.07$) increase in 2-h insulin. None of the coefficient estimates for fasting insulin or HOMA attained statistical significance.

Discussion

In a subsample of women participating in the DEBI randomized controlled pilot trial evaluating the feasibility of a lifestyle intervention for women with gestational diabetes, modest post-partum weight loss in the first year post-partum was associated with improved glucose metabolism; specifically, an attenuated increase in fasting glucose levels and a decrease in 2-h glucose levels. In addition, in analyses adjusted for age, Hispanic ethnicity, medication use in pregnancy, excessive gestational weight gain, breastfeeding at 7 months post-partum and randomized group, there was a positive, significant association between post-partum weight change and fasting and 2-h glucose levels.

The findings of the current study suggest that even modest weight loss [2 kg (4.4 lbs) or greater] in the post-partum period could impede deteriorations in glucose metabolism and possibly delay the development of Type 2 diabetes in women with gestational diabetes. Still, even among women who lost over 2 kg between 6 weeks and 12 months post-partum, fasting glucose, fasting insulin, 2-h insulin and HOMA levels increased, thus emphasizing the need for early and effective interventions for diabetes prevention in women with a recent pregnancy affected by gestational diabetes.

The Diabetes Prevention Program, a randomized controlled clinical trial conducted among men and women with impaired glucose tolerance and elevated BMI, conducted an analysis restricted to those assigned to the intensive lifestyle intervention of healthy diet and physical activity and found that weight loss was the primary predictor of reduced diabetes risk: diabetes incidence was reduced by 16% for every kg of weight lost [17]. Additional research is needed to confirm whether the improvements in glucose metabolism observed in the current study lead to subsequent reductions in the incidence of diabetes following a pregnancy complicated by gestational diabetes.

The principal limitation of this study is the small size of the sample, as the oral glucose tolerance test and blood collection were not initiated until shortly after the pilot trial was already underway. Although women missing the post-partum biomarker measurements did not appreciably differ from those included in the current analyses, these results may not be generalizable to the full DEBI sample. We may have failed to identify a significant association between weight loss and changes in insulin and HOMA because of the small number of women with insulin data available. Insulin has a non-normal, skewed distribution [18], making it difficult to detect small changes over time. Thus, data from larger studies of women with gestational diabetes are needed to validate these findings.

In addition, the current study is cross-sectional in nature; thus, the causal direction of the associations reported cannot be determined. In fact, we found that women who lost weight in the post-partum period began with significantly lower fasting insulin and HOMA values at 6 weeks post-partum. As suggested by Corkey [19], β-cell hypersecretion of insulin may lead to hyperinsulinaemia and insulin resistance, subsequently causing obesity, rather than changes in body weight resulting in downstream effects on insulin secretion, as we hypothesize.

This study suggests that modest post-partum weight loss is associated with improvements in glucose metabolism, as has been reported in other populations at high risk for the development of diabetes. Larger trials with longer follow-up are needed to determine the magnitude of weight loss required for a clinically significant reduction in diabetes risk among women with a recent pregnancy affected by gestational diabetes.

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What's new?

Despite evidence demonstrating the utility of weight loss for diabetes treatment/prevention in high-risk populations of older adults, there is a paucity of data on the association between post-partum weight loss and glucose metabolism in women with gestational diabetes mellitus. This study demonstrates that modest post-partum weight loss is associated with improvements in glucose metabolism, suggesting that post-partum weight loss may be an effective diabetes prevention strategy in this population.

Table 1

Characteristics of women with gestational diabetes by post-partum weight change group: the Diet Exercise and Breastfeeding Intervention (DEBI) study

Characteristic	**Lost weight[†] (*n* = 38)**	**Maintained or gained weight[‡] (*n* = 34)**
Randomized to the lifestyle intervention	21 (55.3)	14 (41.2)
Age at delivery, years		
≤ 34	15 (39.5)	20 (58.8)
≥ 35	23 (60.5)	14 (41.2)
Race–ethnicity[*]		
Non-Hispanic white	14 (36.8)	8 (23.5)
Black/African American	2 (5.3)	2 (5.9)
Asian or Pacific Islander	16 (42.1)	12 (35.3)
Hispanic origin	3 (7.9)	12 (35.3)
Other	3 (7.9)	0 (0.0)
Education[*]		
High school or less	1 (1.4)	4 (5.6)
Some college	5 (6.9)	13 (18.1)
College graduate	15 (20.8)	8 (11.1)
Postgraduate	15 (20.8)	9 (12.5)
Missing	2 (2.8)	0 (0.0)
Parity		
0	13 (34.2)	11 (32.4)
1+	25 (65.8)	32 (67.6)
Medication use in pregnancy		
No medication	25 (65.8)	22 (64.7)
Insulin or insulin plus glyburide	2 (5.3)	4 (11.8)
Glyburide only	11 (29.0)	8 (23.5)
Exceeded the Institute of Medicine’s recommendation for gestational weight gain	14 (36.8)	7 (20.6)
BMI at 6 weeks, kg/m^2		
19–24	15 (39.5)	12 (35.3)
25–29	12 (31.6)	7 (20.6)
30–46	11 (28.9)	15 (44.1)
Breastfeeding at 7 months	24 (63.2)	17 (50.0)
	Mean (SD)	Mean (SD)
Weight at 6 weeks, kg	71.3 (18.1)	75.3 (20.6)
Moderate and vigorous intensity physical activity at 7 months, min per week, *n* = 63	261.7 (150)	280.0 (173)
Fasting glucose at 6 weeks, mmol/l, *n* = 71	5.0 (0.5)	5.1 (0.7)
2-h glucose at 6 weeks, mmol/l	6.4 (1.9)	5.8 (1.5)

Characteristic	**Lost weight[†] (*n* = 38)**	**Maintained or gained weight[‡] (*n* = 34)**
Fasting insulin at 6 weeks[*], pmol/l, *n* = 53	31.6 (18.2)	50.8 (23.0)
2-h insulin at 6 weeks, pmol/l, *n* = 57	212.8 (140.8)	249.4 (136.3)
HOMA-IR[*], *n* = 52	1.1 (0.5)	1.9 (0.9)

[*] $P < 0.05$.

[†] Lost weight = lost > 2 kg between 6 weeks and 12 months post-partum.

[‡] Maintained or gained = lost ≤ 2 kg, or gained weight between 6 weeks and 12 months post-partum.

HOMA-IR, homeostasis model assessment of insulin resistance.

Table 2

Age-adjusted mean levels of plasma glucose, insulin and homeostasis model assessment (HOMA-IR) by post-partum weight change group: the Diet Exercise and Breastfeeding Intervention (DEBI) study.

	Lost weight	**Maintained or gain weight**	***P* for group difference**
	Age-adjusted mean (95% CI)	**Age-adjusted mean (95% CI)**	
Fasting plasma glucose, mmol/l	*n* = 37	*n* = 33	
At 6 weeks	5.0 (4.8–5.2)	5.1 (4.9–5.3)	0.85
At 12 months	5.2 (5.0–5.4)	5.5 (5.3–5.7)	0.02
Change	0.1 (−0.03 to 0.3)	0.4 (0.3–0.6)	0.007
2-h plasma glucose*, mmol/l	*n* = 38	*n* = 33	
At 6 weeks	6.4 (5.8–7.0)	5.8 (5.2–6.4)	0.14
At 12 months	5.5 (5.1–6.0)	6.1 (5.6–6.5)	0.13
Change	−0.9 (−1.4 to −0.3)	0.3 (−0.3 to 0.9)	0.005
Fasting plasma insulin, pmol/l	*n* = 25	*n* = 20	
At 6 weeks	33.3 (24.5–42.2)	50.9 (40.9–60.8)	0.01
At 12 months	47.3 (31.8–62.8)	73.0 (55.5–90.4)	0.04
Change	14.0 (3.4–24.6)	22.1 (10.2–34.1)	0.32
2-h plasma insulin*, pmol/l	*n* = 27	*n* = 23	
At 6 weeks	207.3 (149.8–264.8)	242.3 (179.7–304.9)	0.43
At 12 months	217.3 (140.6–293.9)	423.4 (340.0–506.9)	0.001
Change	10.0 (−56.9 to 76.9)	181.2 (108.3–254.0)	0.001
HOMA-IR	*n* = 24	*n* = 19	
At 6 weeks	1.1 (0.8–1.5)	2.0 (1.6–2.3)	0.001
At 12 months	1.6 (1.0–2.2)	3.1 (2.4–3.7)	0.002
Change	0.5 (0.02–0.9)	1.1 (0.6–1.6)	0.061

*Obtained 2 h after a 75-g oral glucose tolerance test.

Table 3

Adjusted β-coefficients from multiple linear regression analyses estimating the increase in glucose, insulin and HOMA levels associated with a 1-kg increase in weight between 6 weeks and 12 months post-partum; the Diet Exercise and Breastfeeding Intervention (DEBI) study

		Fasting glucose		2-h glucose		Fasting insulin		2-h insulin		HOMA-IR	
Model		**β**	**SE**	**β**	**SE**	**β**	**SE**	**β**	**SE**	**β**	**SE**
1	Age	0.026*	0.012	0.13*	0.042	0.94	0.90	14.378*	5.86	0.056	0.038
2	Model 1 + Hispanic ethnicity	0.029*	0.013	0.13*	0.044	0.59	0.92	12.903*	6.14	0.047	0.041
3	Model 2 + medication use	0.029*	0.013	0.13*	0.043	0.47	0.80	12.864*	6.21	0.034	0.036
4	Model 3 + exceeded the Institute of Medicine's gestational weight gain recommendation	0.025	0.014	0.14*	0.045	0.080	0.79	13.755*	6.50	0.018	0.037
5	Model 4 + breastfeeding	0.029*	0.014	0.14*	0.047	0.30	0.83	12.785	6.69	0.032	0.039
6	Model 5 + randomized group	0.028*	0.013	0.14*	0.046	0.14	0.82	12.509	6.77	0.029	0.039

*$P < 0.05$.

HOMA-IR, homeostasis model assessment of insulin resistance.