Beta-Cell Function and Visceral Fat in Lactating Women With a History of Gestational Diabetes

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Lactation has been recommended as beneficial for the maternal metabolic abnormalities associated with glucose intolerance and diabetes risk, although associations between breastfeeding (BF), glucose tolerance, and adipose tissue distribution are unknown. Therefore, a population of women with recent gestational diabetes (GDM) was evaluated with comparison of results for lactating versus nonlactating women. A total of 26 women participated (14 BF and 12 nonbreastfeeding [nonBF]) with a singleton vaginal delivery after 36 weeks gestation. At 3 months postpartum, each woman completed a 75-g oral glucose tolerance test (OGTT), a frequently sampled intravenous glucose tolerance test (FSIGT), and computed tomography (CT) scanning for adipose distribution and mass. Insulin sensitivity was not significantly different between BF and nonBF groups (4.97 ± 0.78 *v* $3.44 \pm 1.0 \times 10^{-4}$ min^{-1}/(μU/mL) nor was glucose effectiveness (1.92 ± 0.22 *v* $1.56 \pm 0.19 \times 10^{-2}$ min^{-1}). However, the disposition index (DI) (insulin sensitivity [S_I] × acute insulin response to glucose [AIRg]) was higher in the BF group (129.9 ± 26.0 *v* $53.4 \pm 18.0 \times 10^{-4}$ min^{-1}; $P = .03$). Visceral fat (103 ± 14 *v* 97 ± 15 cm^2) and subcutaneous fat (362 ± 36 *v* 460 ± 68 cm^2) were similar between the groups. We conclude that 3 months of BF in a population with previous GDM was associated with improved pancreatic β-cell function, but not with any difference in measures of adiposity.
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GESTATIONAL DIABETES (GDM) is a common and transient glucose intolerance of pregnancy most often resolving at delivery.[1] However, women with GDM remain at an increased risk for postpartum abnormalities in insulin secretion and insulin action, as well as type 2 diabetes.[1-4] Interventions to decrease this risk of progressive glucose intolerance are limited to recommendations pertinent to the general population, wherein diet, exercise, and possibly, sulfonylurea medications[5-7] may be protective. Evidence from animal and human studies suggests that lactation could have beneficial effects on glucose tolerance, maternal weight, and adipose tissue.[8-11] Thus, we questioned whether breastfeeding (BF) could represent a practical primary intervention against insulin resistance and central obesity in women at risk for postpartum glucose intolerance. Therefore, we examined whether lactation was associated with differences in glucose tolerance, insulin sensitivity and secretion, body habits, and adipose tissue in a population of women with a history of GDM.

RESEARCH DESIGN AND METHODS

BF and nonbreastfeeding (nonBF) women with a history of GDM[12] and vaginal delivery of a live singleton infant after 36 weeks gestation were recruited from the practices of participating physicians and offered participation. All women were Caucasian, consistent with local population demographics. After giving informed consent, all women were advised to exercise 3 times a week for 1/2 hour and also to achieve their ideal body weight within 12 months postpartum.

At 3 months postpartum, participants came to the Clinical Investigation Unit on 2 separate occasions, having fasted after midnight. The following were documented at the first visit: heart rate and blood pressure after sitting quietly for 10 minutes, weight gain of pregnancy, infant birthweight, smoking history, hours of weekly exercise, weight, height, waist-hip ratios. Three months postpartum was chosen for evaluation in an effort to minimize the potential variability of frequency and duration of lactation that would ensue as infant diets were supplemented by bottle feeding and solid foods.

Oral Glucose Tolerance Test

Each woman completed an oral glucose tolerance test (OGTT) after 3 days of ad libitum carbohydrate intake. Women in the lactating group were instructed to breastfeed their infant within 2 hours before the OGTT. Baseline blood samples for cholesterol, triglycerides, and glucose were taken, 75 g of oral glucose was given over 10 minutes, and a second blood sample for glucose was drawn at 120 minutes. Impaired glucose tolerance and diabetes were diagnosed by American Diabetes Association (ADA) guidelines.[13]

Frequently-Sampled Intravenous Glucose Tolerance Test

Within 2 weeks of the OGTT, each participant came to the Clinical Investigation Area after a 12-hour fast for a frequently-sampled intravenous glucose tolerance test (FSIGT). Women in the lactating group were again asked to have breastfed their infant within the 2 hours before onset of testing. This testing was performed in the first 2 weeks after a menstrual cycle if the woman had already experienced the return of her menses.

An intravenous line was established in each antecubital fossa and kept open with normal saline. Four baseline samples of blood were drawn through the IV for glucose, insulin, and C-Peptide at times -15, -10, -5, and -1 minutes. A bolus of 50% dextrose was then administered over 1 minute at a dose of 300 mg/kg. Subsequent blood samples for glucose, insulin, and C-peptide were drawn at 2, 3, 4, 6, 8, 10, 12, 14, 16, and 19 minutes after the glucose bolus. Starting at 20 minutes, a bolus injection of regular human insulin at a dose of 0.03 U/kg was given over 1 minute. Blood samples were again taken at 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 100, 120, 140, 160, and 180 minutes. Insulin rather than tolbutamide modification of the FSIGT was chosen, as it was expected some of the women would have already developed diabetes and therefore may have had too small an insulin response to tolbutamide to allow mathematical modelling of results.

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Computed Tomography Scan Determination of Subcutaneous and Visceral Fat

After a negative serum β human chorionic gonadotropin (βhCG), participants underwent computed tomography (CT) scanning for determination of visceral and subcutaneous adipose tissue. A Picker (Cleveland, OH) PQ2000 scanner was used with methodology as previously described.[14] Subjects were scanned supine with arms above the head. CT scout radiograph determined the position of the scans at L4 to L5 level. Total fat area was then outlined by cursor with computer calculation of adipose tissue area within the highlighted area with an attenuation interval for adipose tissue of -30 to -190 HU.[14,15] Deep abdominal fat area was measured by drawing a line within the muscle wall, outlining the abdominal cavity. Abdominal subcutaneous fat area was then calculated as the difference between total fat and deep abdominal fat areas.

Glucose, Insulin, and C-Peptide Assays

Plasma glucose concentrations were determined by glucose oxidase method (Synchron CX Beckman Delta System; Beckman, Irvine, CA). Precision of glucose assay was 2.0% within and 3% between assays at a mean of 5.6 mmol/L. Serum insulin levels were assayed on the Abbott IMx Analyzer (Abbott Labs, Chicago, IL) by microparticle enzyme immunoassay technology. Precision of insulin was 4% within and 4.7% between assays at a mean of 14.5 mU/L. C-Peptide samples were analyzed by RIA (Incstar, Minneapolis, MN). Precision of C-Peptide was 5.7% within and 12.0% between assays at a mean of 460 pmol/L.

Data Analyses

The FSIGT data were analyzed by Bergman's Minimal Model method[16] to provide estimates of insulin sensitivity (S_I) and glucose effectiveness (S_G). First phase insulin response to glucose (AIRg) was determined from the FSIGT as the mean insulin from 2 to 10 minutes minus basal insulin. The disposition index (DI) was calculated as the product of $S_I \times$ AIRg.

Statistical Analysis

Population means were compared by 2-sample *t* tests, as well as Wilcoxon ranked sum test. Correlations were sought between insulin sensitivity parameters and adipose tissue measures, waist-hip ratios, body mass index (BMI), and lipid values. Repeated measures analysis of variance (ANOVA) were used to evaluate results for lactating and nonlactating women. Categorical variables were compared by Fisher's exact test.

RESULTS

Population Characteristics

Twenty-six women participated in the study: 14 who had breastfed for at least 3 months and 12 who had not breastfed past hospital discharge. Groups were matched for age, weight, weight gain of pregnancy, weight at delivery, weight loss by 3 months postpartum, BMI, size of infant, duration of GDM diagnosis, blood pressure, waist-hip ratios, and exercise habits (Table 1).

Glucose Tolerance, Insulin Sensitivity, and Adipose Tissue Results

Lactating and nonlactating women were not different with respect to fasting glucose, fasting insulin, fasting cholesterol, and triglycerides or oral glucose tolerance. In addition, there were no differences in S_I, S_G, or AIRg. However, lactating women did have a significantly higher DI (129.9 ± 26.0 *v* $53.4 \pm 18.0 \times 10^{-4}$ min^{-1}; $P = .03$) implying a significantly higher β-cell function for the degree of insulin resistance. Visceral and subcutaneous adipose volumes were not different between the groups, nor was the ratio of visceral to subcutaneous adipose tissue (Table 2).

Significant correlations were present between S_I and visceral fat ($r = -0.58$, $P = .01$); S_I and subcutaneous fat ($r = -0.70$, $P = .001$) when all BF and nonBF women were considered together. Similarly, there were significant correlations between S_G and subcutaneous fat ($r = -0.50$, $P = .03$); S_G and total body fat ($r = -0.54$, $P = .02$). The DI was not significantly correlated with any of the adipose measures. The nonlactating group alone had significant correlations between S_I and subcu-

Table 1. Population Demographics

	Lactating Women	Nonlactating Women	*P*
No.	14	12	
Age (yr)	30.9 ± 1.3	30.7 ± 1.3	.89
Weight gain during pregnancy (kg)	11.6 ± 1.6	11.2 ± 2.0	.86
Peak pregnancy weight (kg)	86.1 ± 5.4	92.9 ± 7.9	.47
Weight loss by 3 months (kg)	9.2 ± 1.3	10.3 ± 2.8	.69
Weight (kg)	76.8 ± 18.5	72.9 ± 8.0	.67
BMI	30.0 ± 1.9	30.7 ± 2.1	.81
W/H ratio	0.82 ± 0.02	0.81 ± 0.02	.73
Systolic blood pressure (mmHg)	114.3 ± 1.8	118.3 ± 3.7	.33
Diastolic blood pressure (mmHg)	71.8 ± 2.0	73.6 ± 2.4	.57
Infant weight (kg)	3.69 ± 0.20	3.68 ± 2.00	.97
Exercise (h/wk)	1.4 ± 0.6	2.3 ± 0.8	.35
Duration of GDM (wk)	13.2 ± 1.6	13.5 ± 2.5	.92
Smoking	2	1	1.00
On insulin during pregnancy	2	2	1.00
IGT at 3 months	4	2	.64
Diabetic at 3 months	1	3	.59
On OC at 3 months	3	5	.66

NOTE. Results are reported as mean ± SEM.
Abbreviation: OC, oral contraceptive.

Table 2. Insulin, Glucose, and Adipose Measures

	Lactating Women	Nonlactating Women	*P*
Fasting glucose (mmol/L)	5.3 ± 0.3	5.4 ± 0.2	.58
Fasting insulin (pmol/L)	94.2 ± 15.6	86.4 ± 12.0	.70
Cholesterol (mmol/L)	5.0 ± 0.4	4.5 ± 0.3	.27
Triglycerides (mmol/L)	1.3 ± 0.2	2.0 ± 0.4	.12
S_I ($\times 10^{-4}$ min^{-1}/(μU/mL))	4.97 ± 0.78	3.44 ± 1.00	.24
S_G ($\times 10^{-2}$ min^{-1})	1.92 ± 0.22	1.56 ± 0.19	.25
AIRg (μU/mL)	31.9 ± 9.9	18.3 ± 5.6	.26
DI ($\times 10^{-4}$ min^{-1})	129.9 ± 26.0	53.4 ± 18.0	.03
Visceral fat (cm^2)	103 ± 14	97 ± 15	.75
Subcutaneous fat (cm^2)	362 ± 36	460 ± 68	.19
Visceral/subcutaneous fat	0.29 ± 0.03	0.25 ± 0.05	.43

NOTE. DI: AIRg × S_I. Results are reported as mean ± SEM.

Abbreviations: AIRg, acute insulin response to glucose; S_I, insulin sensitivity; S_G, glucose effectiveness.

taneous fat (r = -0.80, P = .01), as well as total body fat (r = -0.80, P = .01). Also, S_G remained significantly correlated with subcutaneous fat (r = -0.68, P = .04) and total body fat (r = -0.70, P = .04), while again DI was not correlated with adipose measures. Lactating women as a separate group had no significant correlations between S_I, S_G, and body fat measures.

DISCUSSION

In this study, BF women had higher insulin secretion at comparable levels of insulin sensitivity as shown by increased values for the DI. However, 3 months of BF was not associated with any differences in body weight, postpartum weight loss, adipose tissue measures, or risk of impaired glucose tolerance and diabetes.

Both AIRg and S_I are determinants of glucose tolerance. It has been proposed that the relationship between AIRg and S_I is hyperbolic,[17] a relationship consistent with the data obtained in our population, as well (Fig 1). Due to this hyperbolic relationship, the DI (AIRg × S_I) is useful to permit assessment of insulin secretion while taking into account the level of insulin sensitivity.[18,19] We found that the DI was higher in lactating women, suggesting that these women were better able to maintain their β-cell function for their degree of insulin resistance.

An increase in β-cell function associated with BF would be consistent with previous reports of nursing women. An observation within a group of lactating women (but without a GDM history) at 8 weeks postpartum found that BF women had lower fasting glucose and insulin levels.[20] Another report from a retrospective survey of a large population of Latino women with GDM concluded that BF was associated with a decrease in both fasting glucose and improved glucose tolerance as determined by the glucose area under the curve from the OGTT.[21] However, unlike this study in Latino women, we did not find a significant difference in insulin levels in the OGTT. While this may reflect our smaller sample size, it may also be due to differing ethnic backgrounds as our Caucasian participants may have had less tendency to insulin resistance. Also, in matching our women for contraceptive use, exercise patterns, timing of acute BF before testing, duration of diabetes, and insulin use during pregnancy, in addition to evaluating all at the same time postpartum, we may have decreased associated confounding effects.

The mechanisms through which lactation has an effect on β-cell function remain speculative. BF is associated with increased metabolic rate,[22,23] so that perhaps there could be associated enhancement of insulin sensitivity and thereby β-cell function. Possibly, there could be direct prolactin effects as levels increase with lactation, and in vitro experiments of islets cultured with prolactin have shown enhanced stimulated insulin secretion.[24] Furthermore, women supplemented with vitamin D have increased insulin secretion raising the possibility that recommendations to drink milk fortified with Vitamin D while breastfeeding could have resulted in an effect on pancreatic function.[25] These or other potential mechanisms responsible for the observed effects of lactation remain to be explored.

While obesity and central body fat are known risks for glucose impairment,[26-31] there has been little previous exploration into an effect of BF on adipose tissue distribution. One observational study of nondiabetic women found a significant weight loss only after 6 months of BF.[10] That study also reported a decrease in suprailiac and subscapular skinfold thickness over 6 months in women who breastfed, although waist/hip measures of central obesity were not reported. There has also been some in vitro experimental evidence suggesting that lactation may influence regional fat tissue metabolism, wherein a study evaluating human abdominal and femoral adipose lipolysis reported lactation was associated with lower extracellular adenosine, raising the possibility that lactation might mobilize lipids preferentially from femoral versus abdominal adipose tissue.[29] In keeping with this, another study reported that femoral fat cells from lactating women exhibited increased lipolysis.[30]

In contrast to the clinical implications of the foregoing indirect evidence, our women had no differences in postpartum weight loss, BMI, waist-hip ratios, and CT measures of adipose tissue. This may be due to better matching for exercise and contraceptive use than previously reported, but also, we have measured central adipose measures more directly than any previous reports through using waist-hip ratios and radiologic

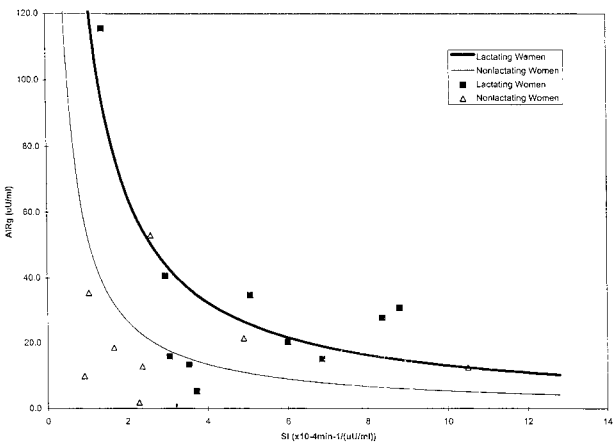

Fig 1. AIRg *v* S_I in lactating and nonlactating women.

imaging. In addition, it may be that women with a history of GDM have different responses to BF than the nondiabetic populations, which have been reported to this point. Finally, 3 months of lactation may have been insufficient time to result in significant body habit alterations. Our findings are consistent with other reports in which lactation was either not significantly associated with postpartum weight loss or, at most, only weakly correlated.[11,31]

The present study was not designed to investigate the issue of oral contraceptive (OC) use and glucose tolerance, although 8 of our participants had returned to a birth control pill for 1 month before testing. A previous retrospective study of OC use in women with antecedent GDM reported there was no increased risk of postpartum diabetes when women used combination estrogen and progesterone OC in comparison to women using nonhormonal contraception.[32] Progestin-only OC were associated with an increased risk of type 2 diabetes mellitus, but all BF women who wanted hormonal contraception were given the progestin-only pill, therefore, no conclusions could be drawn about lactation and use of combination OC. All OC used by our study women were estrogen and progesterone combinations in keeping with local practice, and similar numbers of our BF and nonBF women decided to use them. Although the numbers were evidently small, we did compare OC users versus non-OC users in BF and nonBF groups and found no significant differences between them.

In summary, we conclude that within a matched population of women with a history of GDM, 3 months of BF was associated with improved pancreatic β-cell function, but not with any significant differences in glucose tolerance, adipose tissue mass, or adipose distribution.

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REFERENCES

1. O'Sullivan JS: Gestational diabetes: Unsuspected asymptomatic diabetes in pregnancy. N Engl J Med 264:1082-1085, 1961

2. Ryan EA, Imes S, Liu D, et al: Defects in insulin secretion and action in women with a history of gestational diabetes. Diabetes 44: 506-512, 1995

3. Metzger BE, Bybee DE, Freinkel N, et al: Gestational diabetes mellitus: Correlations between the phenotypic and genotypic characteristics of the mother and abnormal glucose tolerance during the first year post-partum. Diabetes 34:111-115, 1985 (suppl 2)

4. Dornhorst A, Bailey P, Anyaoku V, et al: Abnormalities of glucose tolerance testing following gestational diabetes. Q J Med 77:1219-1228, 1990

5. Long SD, O'Brien K, Swanson M, et al: Weight loss prevents the progression of impaired glucose tolerance to non-insulin dependent diabetes mellitus: Ten year longitudinal study. Diabetes 41:72A, 1992 (suppl 1, abstr)

6. Manson JE, Nathan DM, Krolewski AS, et al: A prospective study of exercise and incidence of diabetes among US male physicians. JAMA 268:63-67, 1992

7. Sartor G, Schersten B, Carlstrom S, et al: Ten-year followup of subjects with impaired glucose tolerance: Prevention of diabetes by tolbutamide and diet regulation. Diabetes 29:41-49, 1990

8. Jones RG, Ilic V, Williamson DH: Physiological significance of altered insulin metabolism in the conscious rat during lactation. Biochem J 220:455-460, 1984

9. Burnol A-F, Leturque A, Ferre P, et al: Increased insulin sensitivity and responsiveness during lactation in rats. Am J Physiol 251: E537-E541, 1986

10. Brewer MM, Bates MR, Vannoy LP: Postpartum changes in maternal weight and body fat depots in lactating vs nonlactating women. Am J Clin Nutr 61:149-153, 1989

11. Dugale AE, Eaton-Evans J: The effect of lactation and other factors on post-partum changes in body weight and triceps skinfold thickness. Br J Nutr 61:149-153, 1989

12. American Diabetes Association: Gestational diabetes: Position statement. Diabetes Care 9:430, 1986

13. American Diabetes Association: Screening for type 2 diabetes. Diabetes Care 21:20-22, 1998 (suppl 1)

14. Sjostrom L, Kvist H, Cederblad A, et al: Determination of total adipose tissue and body fat in women by computed tomography, ^{40}K and tritium. Am J Physiol 250:E736-45, 1986

15. Kvist H, Tylen U, Sjostrom L: Adipose tissue volume determinations in women by computed tomography: Technical considerations. Int J Obes 10:53-67, 1986

16. Bergman RN: Toward physiological understanding of glucose tolerance. Minimal model approach. Diabetes 38:1512-1527, 1989

17. Kahn SE, Prigeon RL, McCulloch DK, et al: Quantification of the relationship between insulin sensitivity and β-cell function in human subjects. Diabetes 42:1663-1672, 1993

18. Watanabe RM, Valle T, Hauser ER, et al: Familiarity of quantitative metabolic traits in Finnish families with non–insulin-dependent diabetes mellitus. Finland-United States Investigation of NIDDM Genetics (FUSION) Study investigators. Hum Hered 49:159-168, 1999

19. Dunaif A, Finegood DT: Beta-cell dysfunction independent of obesity and glucose intolerance in the polycystic ovary syndrome. J Clin Endocrinol Metab 81:942-947, 1996

20. Lenz S, Kuhl C, Hornnes P, et al: Influence of lactation on oral glucose tolerance in the puerperium. Acta Endocrinol 98:428-431, 1981

21. Kjos SL, Henry O, Lee RM, et al: The effect of lactation on glucose and lipid metabolism in women with recent gestational diabetes. Obstet Gynecol 82:451-455, 1993

22. Motil KJ, Montandon CM, Garza C: Basal and postprandial metabolic rates in lactating and nonlactating women. Am J Clin Nutr 52:610-615, 1990

23. Butte NF, Hopkinson JM, Mehta N, et al: Adjustments in energy expenditure and substrate utilization during late pregnancy and lactation. Am J Clin Nutr 69:299-307, 1999

24. Crepaldi SC, Carneiro EM, Boschero AC: Long-term effect of prolactin treatment on glucose-induced insulin secretion in cultured neonatal rat islets. Horm Metab Res 29:220-224, 1997

25. Bocher BJ, Mannan N, Noonan K et al: Glucose intolerance and impairment of insulin secretion in relation to vitamin D deficiency in east London Asians. Diabetologia 38:1235-1245, 1995

26. Kissebah AH, Vydelingum N, Murray R, et al: Relation of body fat distribution to metabolic complications of obesity. J Clin Endocrinol Metab 54:254-260, 1982

27. Werbel SS, Faulk KL, Terry JG, et al: Intra-abdominal fat by MRI scanning: Relationship to insulin resistance and age according to gender. Diabetes 43:53A, 1994 (suppl 1, abstr)

28. Hartz AJ, Rupley DC, Rimm AA: The association of girth measurements with disease in 32,545 women. Am J Epidemiol 119: 71-80, 1984

29. Stoneham S, Kiviluoto T, Keso L, et al: Adenosine and the regional differences in adipose tissue metabolism in women. Acta Endocrinol 118:327-331, 1988

30. Rebuffe-Scrive M, Enk L, Crona N, et al: Fat cell metabolism in different regions in women. J Clin Invest 75:1973-1976, 1985

31. Ohlin A, Rossner S: Maternal body weight development after pregnancy. Int J Obes 14:159-173, 1990

32. Kjos SL, Peters RK, Xiang A, et al: Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes. JAMA 280:533-538, 1998