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ORIGINAL RESEARCH

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Abstract

Purpose: To determine the associations between glycated hemoglobin (A1C) values at three, 12 and 24 months postpartum taken during the Families Defeating Diabetes trial.

Methods: The Families Defeating Diabetes trial was a randomized 12 month lifestyle intervention delivered in the first year postpartum. Women were reviewed at three, 6 12 and 24 months for body habitus, diet and lifestyle choices. Glycated hemoglobin levels were measured at three, 12 and 24 months.

Results: There were 170 randomization participants: 89 interventional (INT); and 81 control (CON). Of these 170 participants, 50 INT and 47 CON completed 12-month follow-up and 26 INT and 24 CON completed 24-month follow-up. Study outcomes did not differ between the cohorts. Combined intraclass correlation coefficients for reliability of repeated results showed substantial reliability: 0.74 (95% CI 0.63, 0.83) between three and 12 month A1C; and 0.72 (95% CI 0.51, 0.85) for three and 24 month A1C. Pearson correlations for three month vs 12 month A1C were r=0.745 (p<0.001) and three month vs 24 month A1C were r=0.718 (p=0.001)

Conclusions: The A1C values at three, 12 and 24 months after gestational diabetes mellitus showed substantial reliability by intraclass correlation coefficients analysis as well as significant Pearson correlations. These findings add perspective to timing and use of A1C to document postpartum glucose tolerance for women with recent gestational diabetes mellitus. These findings suggest a role for postpartum A1C testing; however, a longitudinal comparison with OGTT results is required to confirm clinical validity.

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Women with gestational diabetes mellitus (GDM) are at significantly increased risk not only for recurrent GDM and metabolic syndrome [1] but for developing type 2 diabetes [2,3]; therefore, postpartum glucose tolerance assessment is strongly recommended [4,5]. Despite much effort, achieving more than a 50% completion rate for postpartum oral glucose tolerance testing (OGTT) has been challenging [6,7].

The use of glycated hemoglobin (A1C) levels as an alternative to OGTT for diagnosing prediabetes and diabetes has associated convenience, but has also generated controversy in GDM follow-up (8,9) as well as in defining which A1C value is reliably associated with impaired glucose tolerance and/or impaired fasting glucose within wider populations [10,11]. Despite these debates, clinical practice guidelines, including those from the American Diabetes Association and Diabetes Canada, identify the A1C as a screening tool with utility for both diabetes and prediabetes in non-pregnant and postpartum settings [12,13]. Therefore, it was of interest whether successive A1C values taken after GDM would show any reliable relationship over time.

Families Defeating Diabetes (FDD) was a 12 month Canadian randomized controlled trial of a postpartum healthy living intervention for women with recent GDM, and included a 24 month final study contact [14]. Although the FDD intervention was not associated with significant changes in the main outcomes of interest at 12 months (body habitus, lifestyle choices or A1C measures between interventional (INT) and control (CON)), blood samples for A1C testing were collected at three, 12 and 24 months as part of the study protocol.

Relationships between repeated lab measurements can be expressed through analysis of intraclass correlations (ICC), which indicate how strongly results within the same group resemble each other, as well as by analysis of Pearson correlations, which reflect the relatedness of results in each pair of individuals [15,16]. Both ICCs and Pearson correlations for the GDM study's A1C values are presented here with the aim to inform decisions of timing and options for postpartum dysglycemia testing.

Methods

Participants

Methods and results were published previously [14]. In summary, English-speaking, overweight women with GDM were recruited during late pregnancy or early after delivery from three Canadian sites: London, Ontario; Calgary, Alberta; and Victoria, British Columbia. The study was approved by the site Ethics Committee and registered at Clinicaltrials.gov as NCTO1425645; Families Defeating Diabetes. After informed consent, women were randomized to intervention (INT, N=89) or control group (CON, N=81). The intervention was 12 months in duration, with visits at three and 12 months, followed by a final contact at 24 months.

Measurements

Non-fasting blood samples for hemoglobin (A1C) were taken from maternal participants at three, 12 and 24 months for local analysis. The A1C test measures the amount of hemoglobin with attached glucose, and reflects average blood glucose levels over the previous three months. Measurements are expressed as a percentage. Non-diabetic range for A1C was <6.5% at all sites. The A1C measurement was chosen over OGTT to assess study glucose tolerance for pragmatic compliance reasons: 1) A1C was more convenient than asking women to accept three iterations of OGTT testing during the 24 months of study follow up; 2) A1C could be measured at any time of day allowing combination with other study tasks and participants were not restricted to early morning appointments; and 3) prior reports had discouragingly poor OGTT attendance rates despite active encouragement [6,7,17,18].

Statistical analysis

Between-group comparisons for A1C levels were made using unpaired t-tests and between group differences were unadjusted. Intraclass correlation coefficients (ICC) are used for evaluation of test-retest agreement. ICC point estimates and 95% two-sided confidence intervals (CIs) were determined using one-way analysis of variance (ANOVA) models. Confidence intervals were obtained by using the approximate F-distribution. Study results were interpreted according to Landis and Koch (19) where ICCs of <0.2 indicate poor or slight agreement; 0.21-0.4 indicate fair agreement; 0.41-0.6 indicate moderate agreement; 0.61-0.8 indicate substantial agreement; >0.8 indicate almost perfect agreement. Furthermore, Pearson correlations were calculated for A1C at three, 12 and 24 months. Associations were sought between A1C and breastfeeding, maternal weight, maternal waist circumference, weight loss and family income. All statistics were calculated using SAS software and significance was accepted at $p \leq 0.05$.

Results

Of the 170 women who were recruited for the study, 97 completed 12 months of the study, and 75 of the 97 had A1C results (INT N=39/50; CON N=36/47). Women were predominantly Caucasian (71%). Results were excluded from

the four women were pregnant at the 12 month visit (three INT, one CON). Two INT women were using metformin for fertility or menstrual issues, but without a diagnosis of DM. Two CON women reported an intervening diagnosis of DM, one of whom was on insulin and pregnant (excluded, as noted above) and the other being the sole study woman with an A1C >6.4% (7.2%). Equal numbers of INT and CON women had undergone delivery by caesarian section (seven women in each cohort). The A1C values did not differ between INT and CON women at three, 12 or 24 months follow-up (Table 1). The A1C values at the 3-month follow-up for women who dropped out of the study did not differ significantly from that of women who completed the 12-month follow-up: 5.8±1.2% compared with 5.5±0.4%; p=0.082. The ICCs were 0.74 (95% CI: 0.63, 0.83) for three and 12 months and 0.72 (95% CI 0.51, 0.85) for three and 24 months (INT and CON cohorts combined).

TABLE 1. Glycated hemoglobin values measured at three, 12 and 24 months

	INT	CON	p-value
3 months	5.5±0.4% N=89	5.4±0.5% N=81	0.301
12 months	5.5±0.03% N=39	5.5±0.5% N=36	0.885
24 months	5.6±0.3% N=16	5.3±0.5% N=16	0.154

Abbreviation: CON, control; INT, interventional
Results presented as mean±SD.

Pearson correlations for A1C values at three and 12 months were significant: r=0.745, p<0.001 (INT and CON cohorts combined). Furthermore, although numbers were small, the 24 month A1C results remained significantly correlated with both three and 12 month results (Table 2).

The A1C values were not associated with number of months spent breastfeeding, maternal weight, maternal waist circumference or weight loss. The A1C values were found to be higher in women reporting a family history of diabetes at 12 months (positive family history: 5.6±0.5% compared with negative family history: 5.4±0.3%, p=0.01) as well as 24 months (positive family history: 5.7±0.3% compared to negative family history: 5.3±0.05%, p=0.04).

Table 2. Pearson correlations for glycated hemoglobin levels measured at three, 12, and 24 months

Cohort	3 months	12 months
Combined CON and INT cohorts		
3 months	-	-
12 months	0.745*	-
24 months	0.718*	0.784*
CON cohort		
3 months	-	-
12 months	0.817*	-
24 months	0.741**	0.789*
INT cohort		
3 months	-	-
12 months	0.594*	-
24 months	0.703*	0.836*

Abbreviation: CON, control; INT, interventional
*p<0.001; ** p<0.002

Discussion

Glycated hemoglobin values at three, 12 and 24 months in women with recent GDM were found to have substantial reliability by ICC analysis, as well as exhibit significant Pearson correlation. We concluded that A1C values were significantly correlated at three, 12 and 24 months in women with recent GDM, supporting a possible clinical role for A1C in documenting postpartum glucose tolerance as early as three months postpartum.

Current practice guidelines recommend that women with GDM undergo a postpartum OGTT between 4/6 weeks and six months [4,5]. Significant efforts have been made to encourage postpartum OGTT testing with varying reminder cues for patients and/or physicians, yet compliance rates are rarely higher than 50% [6,7,17,18]. In addition to the presumed underlying anxiety about having a test result in the diabetes range, barriers to postpartum OGTT testing may include the following: having to remain quiet for the 2-hour lab test; fasting in a busy household; accessing early morning child care; and caring for a small child in a lab waiting room [20].

Although the foregoing practical issues might be ameliorated somewhat by using a random A1C testing versus OGTT, there has been clinical discomfort with using A1C testing after GDM due to potentially confounding issues, including red cell turnover soon after delivery, as well as lack of sensitivity compared with OGTT especially in defining prediabetes states of impaired glucose tolerance or impaired fasting glucose [21,22]. While the OGTT is the historical postpartum gold standard, as a test it may not be highly reproducible [23,24].

Although reassuring that A1C values as early as three months showed significant correlations with the 12 and 24 month results, this finding may not be surprising as Pearson correlation analyses compare each subject with herself over time [15,16]. However, the ICC analysis revealed that A1C levels were also in "substantial" reliability for both three and 12 months as well as three and 24 months. These results may add some reassurance to decisions surrounding postpartum glycemia test choice and timing as A1C results taken at the three study intervals over two years were significantly related, including samples taken as early as three months.

The study has acknowledged limitations. The A1C results represent a post hoc analysis as FDD was not designed nor powered to compare A1C testing with OGTT. Participants rarely had A1C results that were out of normal ranges so conclusions may not apply to a more glucose intolerant population. Participants were predominantly Caucasian without suspected hemoglobin abnormalities so results may not apply to more diverse populations. Furthermore, while results for the 14 women who had undergone a caesarian section were included in the analyses, estimated blood loss at delivery and concurrent hemoglobin levels were not documented. Therefore, conclusions may not apply to women with significant postpartum blood loss or ongoing anemia.

The results for ICC reliability and Pearson correlations between A1C values at three, 12 and 24 months would support some utility in using A1C to assess glycemic balance postpartum. Glycated hemoglobin is an accepted screening tool for diagnosing dysglycemia in the general population [12,13] and healthy women fully recovered from any associated blood loss after a recent GDM pregnancy should not differ from the background population deemed appropriate for A1C screening. The principles used in choosing A1C testing in this FDD study can also apply to real world postpartum follow up as A1C testing eliminates the maternal barriers associated with OGTT tests such as preparatory carbohydrate loading, followed by fasting, and then attending a two-hour lab test. While this report illustrates the reliability of repeated A1C testing after GDM, confirmation of its clinical validity would depend upon a further investigation wherein A1C testing and fasting OGTT are performed longitudinally in a larger and more diverse population.

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