Pregravid HbA_{1c} and Glucose Measurement to Rule Out Future Gestational Diabetes Mellitus and Reduce the Need for Oral Glucose Tolerance Testing in Pregnancy

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The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) has recommended universal screening for gestational diabetes mellitus (GDM) by oral glucose tolerance test (OGTT) in all pregnant women (1). However, concern has been raised that this recommendation may pose a resource challenge for health care systems (2). Recognizing that women who develop GDM have chronic metabolic dysfunction that predates their pregnancy (3), we hypothesized that measurement of pregravid HbA_{1c} or glucose may provide the capacity to rule out GDM in low-risk women and thereby reduce the overall OGTT burden in pregnancy.

To test this hypothesis, we conducted a population-based retrospective cohort study using real-world data for Ontario, the most populous province in Canada. With administrative databases that track health care utilization, we identified all women in Ontario without preexisting diabetes who had pregravid measurement of HbA_{1c} or glucose before singleton live-birth pregnancies between January 2008 and December 2015. Pregravid HbA_{1c} or glucose was measured at median 1.4 years (interquartile range 1.03–2.05 years) before pregnancy in 334,829 women, including 20,221 who developed GDM. For this study, the women were randomly assigned to either derivation (n = 167,401) or validation (n = 167,428) cohorts to evaluate the capacity of these pregravid glycemic measurements for predicting GDM. In the derivation cohort, pregravid HbA_{1c} was the strongest predictor of GDM (odds ratio 7.30, 95% CI 6.57–8.11), followed by fasting glucose (3.11, 2.94–3.30) and random glucose (1.63, 1.58–1.68) (adjusted for age, ethnicity, income, and rurality). The odds of GDM increased by 22% for each 0.1% (1 mmol/mol) rise in pregravid HbA_{1c}. Area under receiver-operating-characteristic curve was higher for HbA_{1c} (0.680) than for fasting glucose (0.648) or random glucose (0.623). Thus, among these pregravid glycemic measures, HbA_{1c} emerged as the best predictor of subsequent GDM.

To determine a pregravid HbA_{1c} threshold below which the need for an antepartum OGTT could be obviated without missing an excessive proportion of GDM cases, we first identified the HbA_{1c} threshold at which the negative predictive value (NPV) for ruling out GDM was optimized in the derivation cohort. The NPV for ruling out GDM was optimized (NPV = 98.2%) at pregravid HbA_{1c} ≤4.5% (26 mmol/mol). However, in the validation cohort, this HbA_{1c} threshold only reduced the need for antepartum OGTT in 0.3% of women (Table 1). Conversely, if sensitivity for predicting GDM was set at 95% in the derivation cohort, the resultant threshold of pregravid HbA_{1c} ≤5.1% (32 mmol/mol) would reduce the need for OGTT in 12.7% of women in the validation cohort but at the cost of missing 4.9% of GDM diagnoses (Table 1). Indeed, review of the clinical implications if women below a specified pregravid HbA_{1c} threshold did not have an antepartum OGTT (last two columns of Table 1) revealed that there was no HbA_{1c} threshold that provided a meaningful reduction in the number of OGTTs without missing an excessive proportion of GDM diagnoses. Thus, although pregravid HbA_{1c} is a robust predictor of GDM, the test characteristics are clinically unacceptable for reducing the need for GDM screening by OGTT in pregnancy.

A strength of this study is the population-based design using real-world data collected in clinical care within the multiethnic

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Table 1—Test characteristics of HbA_{1c} thresholds from 4.0% to 6.4% (20 to 46 mmol/mol) for predicting subsequent GDM in the validation cohort and clinical implications if women with pregravid HbA_{1c} at or below the indicated threshold do not have OGTT in pregnancy

HbA_{1c} threshold		Test characteristics for predicting subsequent GDM				Clinical implications if women with HbA_{1c} at or below the threshold do not have OGTT	
HbA_{1c} (%)	HbA_{1c} (mmol/mol)	Sensitivity	Specificity	PPV	NPV	Proportion of OGTTs avoided	Proportion of GDM cases missed
4.0	20	100.0%	0.0%	7.9%	95.8%	0.0%	0.0%
4.1	21	100.0%	0.1%	7.9%	97.1%	0.1%	0.0%
4.2	22	100.0%	0.1%	7.9%	97.8%	0.1%	0.0%
4.3	23	99.9%	0.1%	7.9%	95.9%	0.1%	0.1%
4.4	25	99.9%	0.2%	7.9%	96.5%	0.2%	0.1%
4.5	26	99.9%	0.3%	7.9%	97.3%	0.3%	0.1%
4.6	27	99.7%	0.6%	7.9%	96.4%	0.6%	0.3%
4.7	28	99.5%	1.1%	7.9%	96.2%	1.0%	0.5%
4.8	29	99.1%	2.1%	8.0%	96.4%	2.0%	0.9%
4.9	30	98.3%	4.2%	8.1%	96.7%	4.0%	1.7%
5.0	31	97.4%	7.7%	8.3%	97.2%	7.3%	2.6%
5.1	32	95.1%	13.3%	8.6%	96.9%	12.7%	4.9%
5.2	33	91.4%	21.5%	9.1%	96.7%	20.5%	8.6%
5.3	34	85.7%	32.4%	9.8%	96.3%	30.9%	14.3%
5.4	36	77.8%	45.1%	10.8%	95.9%	43.3%	22.2%
5.5	37	68.1%	58.7%	12.4%	95.6%	56.6%	31.9%
5.6	38	57.2%	71.4%	14.7%	95.1%	69.2%	42.8%
5.7	39	44.6%	81.9%	17.5%	94.5%	79.8%	55.4%
5.8	40	33.2%	89.4%	21.2%	94.0%	87.6%	66.8%
5.9	41	22.6%	94.2%	25.2%	93.4%	92.9%	77.4%
6.0	42	14.6%	97.1%	30.0%	93.0%	96.2%	85.4%
6.1	43	8.7%	98.6%	34.6%	92.6%	98.0%	91.3%
6.2	44	4.9%	99.4%	40.6%	92.4%	99.0%	95.1%
6.3	45	2.6%	99.7%	47.2%	92.3%	99.6%	97.4%
6.4	46	1.0%	99.9%	53.5%	92.2%	99.8%	99.0%

PPV, positive predictive value.

society of Ontario, such that the findings should be generalizable to other settings. A limitation is that the reason for these pregravid glycemic measurements cannot be definitively ascertained (i.e., whether ordered as routine care or for a clinical reason). However, while clinical indications theoretically could have biased toward a higher-risk cohort, it is notable that the test characteristics of pregravid HbA_{1c} were still insufficient to reliably rule out GDM even in that potential setting.

The current findings also hold clinical implications. Specifically, these findings suggest that, while insufficient to rule in or rule out GDM on an individual basis, pregravid HbA_{1c} measurement can identify a subpopulation of women at higher risk of developing GDM. Indeed, as trials of lifestyle intervention initiated in early pregnancy have been largely unsuccessful in reducing the incidence of GDM, it has been suggested that preconception intervention may be more appropriate (4). In this context, pregravid HbA_{1c} measurement could enable the recruitment of a cohort of women at higher risk of GDM in whom preconception lifestyle intervention could be evaluated in a prevention trial. Moreover, since intrauterine biochemical changes and fetal overgrowth precede the clinical diagnosis of GDM in late 2nd trimester (5), the preconception identification of high-risk women may enhance both early intervention and clinical monitoring.

In conclusion, pregravid HbA_{1c} and glucose levels can predict a woman's future risk of GDM. However, their test characteristics are clinically unacceptable for reducing the need for GDM screening by OGTT in pregnancy.

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of the data and the accuracy of the data analysis.

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