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Abstract

***Aims*:** To investigate the performance of early pregnancy HbA_{1c} for predicting gestational diabetes mellitus (GDM) and adverse pregnancy outcomes in obese women.

***Methods*:** Post hoc analysis using data from the Vitamin D And Lifestyle Intervention for GDM prevention trials conducted across 9 European countries (2012–2014). Pregnant women (BMI ≥ 29 kg/m^2) underwent a baseline HbA_{1c} and oral glucose tolerance tests at < 20 weeks, 24–28 weeks, and 35–37 weeks. Women with GDM were referred for treatment.

***Results*:** Among the 869 women tested, the prevalence of GDM was 25.9% before 20 weeks, with a further 8.6% at 24–28 weeks. The areas under the curves for HbA_{1c} at the two time points were 0.55 (0.50–0.59) and 0.54 (0.47–0.61), respectively. An early HbA_{1c} ≥ 5.7% (39 mmol/mol) (N = 111) showed low sensitivity (18.2%) with 89.1% specificity for GDM before 20 weeks, at 24–28 weeks (sensitivity of 8.0% and specificity of 88.6% after excluding early GDM), and throughout gestation (sensitivity of 15.9% and specificity of 89.4%). The ≥ 5.7% (39 mmol/mol) threshold was significantly associated with concurrent GDM before 20 weeks (adjusted OR (aOR) 2.77(1.39–5.51)) and throughout gestation (aOR 1.72 (1.02–2.89)), but not adverse pregnancy outcomes.

***Conclusions*:** Early pregnancy HbA_{1c} is of limited use for predicting either GDM or adverse outcomes in overweight/obese European women.

Keywords: Diagnostic threshold; Gestational diabetes mellitus; Hemoglobin A_{1c}; Odds Ratio; Pregnancy; Pregnancy outcome

1 Introduction

The prevalence of gestational diabetes mellitus (GDM) has been rising worldwide with the growing epidemic of obesity, advancing maternal age, and redefined diagnostic approaches endorsed by the International Association of Diabetes in Pregnancy Study Groups (IADPSG) [1–3]. Glycated hemoglobin (HbA_{1c}) reflects average blood glucose over a period of 2 to 3 months depending on red blood cell longevity and is a possible tool for identifying pregnant women who are more likely to have, or to develop, GDM and adverse pregnancy outcomes. HbA_{1c} has been recommended as a diagnostic test for detecting diabetes in early pregnancy, but its accuracy for diagnosing GDM is questionable [4]. Several factors affect the correlation of HbA_{1c} with glycemia, including age, genetic background, and environmental factors [5]. Conditions that interfere with the red blood cell survival rate, haemoglobinopathies, glycation, and different HbA_{1c} assays also complicate interpretation [5].

In pregnancy, the HbA_{1c} is naturally lower than in the non-pregnant state due to changes in erythrocyte lifespan and a decrease in plasma glucose level [6–8]. Furthermore, the HbA_{1c} varies throughout normal pregnancy and between different ethnic groups [6,9]. Several studies have evaluated the utility of early pregnancy HbA_{1c} for GDM prediction including a number that tested the use of a non-pregnant pre-diabetes threshold (5.7% (39 mmol/mol)) [10,11], while others proposed a threshold of 5.9% (41 mmol/mol) for diagnosing hyperglycemia and identifying a subgroup of pregnant women who are at greater risk of adverse pregnancy outcomes [12,13]. Some local practices treat women whose booking HbA_{1c} is in the prediabetes range as if they have GDM without labelling them as such [14]. However, while this cut point is sometimes used clinically, there is no widespread adoption, reflecting doubt about its usefulness. We now examine the utility of an early pregnancy HbA_{1c} as a continuous variable, and at a threshold of 5.7% (39 mmol/mol) for detecting GDM before 20 weeks, at 24–28 weeks and at 35–37 weeks based on IADPSG criteria and to predict GDM-related outcomes in overweight/obese pregnant women.

2 Materials and methods

This study is a post-hoc analysis of the vitamin D And Lifestyle Intervention for GDM prevention (DALI) trial (registration number ISRCTN70595832), which was conducted across 11 centres in nine European countries between 2012 and 2014. The trial compared different lifestyle interventions for reducing GDM risk among overweight/obese pregnant women. The trial protocol has been described elsewhere [15]. Eligible participants were women with singleton pregnancies, aged over 18 years old, with a body mass index of ≥ 29 kg/m^2 who were attending a participating antenatal clinic before 20 weeks of gestation. Women with pre-existing diabetes, psychiatric and chronic medical conditions, language barriers, or the inability to perform lifestyle interventions were ineligible. Each site obtained local ethics approval from the respective ethics committee. All participants underwent a clinical and laboratory assessment before 20 weeks, 24–28 weeks and 35–37 weeks.

2.1 Laboratory analyses

2.1.1 OGTT xxx

A 2-hour, 75-gram oral glucose tolerance test (OGTT) was carried out at baseline, 24–28 weeks, and 35–37 weeks following standardized methodology [15]. Women were advised to fast for 10 h before the scheduled test. Venesections were performed at 0, 60, and 120 min (mins) after consumption of 250 ml of 75 g glucose solution. Blood specimens were collected into sodium fluoride tubes and centrifuged and separated within 20–30 mins at 2470 g/10 mins at a temperature of 4 °C. The plasma portion was then pipetted into micronic loborack and frozen in 250 µl aliquots at −20 °C until further processing. The glucose was measured in the local laboratories as well as in the central trial laboratory in Graz, Austria. Glucose assay was performed using the hexokinase method (DiaSys Diagnostic Systems, Holzheim, Germany), which has an analytical sensitivity of 0.1 mmol/L. Results from the local laboratories were used to assess the eligibility for participant's inclusion in the trial and to provide immediate referral for GDM management. The central laboratory OGTT results were used for the study analysis. GDM was defined as per the IADPSG criteria (i.e., fasting glucose ≥ 5.1 mmol/l or 1-hour glucose ≥ 10.0 mmol/l or 2-hour glucose ≥ 8.5 mmol/l) [16].

2.1.2 HbA_{1c}

HbA_{1c} was quantified in a certified (ISO 9001:2015) central laboratory in whole EDTA-anticoagulated blood by high-performance liquid chromatography using an ADAMS HA-8180 V automated analyser from Menarini Diagnostics (Vienna, Austria). The intra- and inter-assay coefficients of variation were 1.2% and 2.6% at 41 mmol/mol (5.9%) and 0.6% and 2.9% at 95 mmol/mol (10.8%), respectively. Samples were frozen at −80 °C.

2.2 Intervention

Women fulfilling the criteria for GDM by IADPSG criteria were excluded from the DALI interventions and received treatment as per local practice guidelines. Where the OGTT from such excluded women did not fulfil local GDM criteria, no treatment was provided unless GDM was diagnosed at 24–28 weeks or on the decision of local clinicians. Women without GDM, pre-stratified by site, were randomly allocated to eight groups (healthy eating (HE); physical activity (PA); HE and PA; usual care; HE, PA, and vitamin D (Vit D); HE, PA, and placebo; Vit D alone; placebo alone) as previously described [17,18]. Lifestyle intervention encompassed information on the risks of GDM and pregnancy weight gain together with standardized and culturally tailored coaching on healthy eating and/or physical activity, delivered through a combination of face-to-face meetings and telephonic means (text messages, phone calls). These interventions were shown to have no significant effect on either the prevention of GDM or adverse pregnancy outcomes [17,18].

Women were excluded from the analyses if their OGTT and HbA_{1c} results were diagnostic of overt diabetes. Demographic and clinical information were collected using a questionnaire. The main outcome measure for this study was the development of GDM. Secondary pregnancy outcomes included spontaneous abortion (before 22 weeks), birth weight over 4 kg, large for gestational age (LGA) (defined as birth weight > 90th percentile), small for gestational age (SGA) (defined as birth weight < 10th percentile), preeclampsia, pregnancy induced hypertension (PIH), preterm birth (<37 weeks), cesarean section, hyperbilirubinemia, Neonatal Intensive Care Unit (NICU) stay, weight gain under 5 kg, and induction of labour (use of prostaglandins). Pregnancy outcomes were obtained from the medical records.

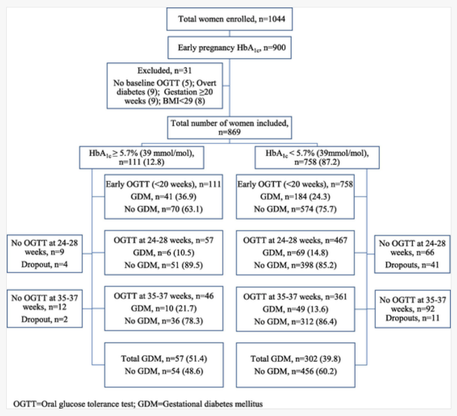
2.3 Statistical analysis

Continuous data were tested for a normal distribution and presented as means and standard deviations. An independent samples *t*-test was used to compare means. Categorical data were presented as percentages and compared using the chi-square test or Fisher's Exact test. The HbA_{1c} groups were created using the prediabetes threshold of 5.7% (39 mmol/mol). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were estimated using cross tabulation. The association between higher HbA_{1c} ≥ 5.7% (39 mmol/mol) and adverse pregnancy outcomes was measured using odds ratios and 95% confidence intervals in a binary logistic regression analysis. Results were controlled for potential confounding factors such as maternal age, pre-pregnancy BMI, booking BMI, family history of diabetes, country, randomisation group, GDM status, and GDM treatment. A receiver operating characteristic (ROC) analysis was performed to determine the predictive ability of HbA_{1c} for GDM and adverse pregnancy outcomes. The ROC curve was constructed by plotting sensitivity against 1- specificity for all possible thresholds using HbA_{1c} as a continuous variable. A p value of < 0.05 was accepted as a cut-off for statistical significance. To assess the ability of HbA_{1c} for predicting GDM using higher glycemic thresholds, we performed sensitivity analyses using a fasting glucose of ≥ 6.1 mmol/l (110 mg/dl), in both the first [19] and second trimester (13–20 weeks). In the sensitivity analysis, we also explored if changing the HbA_{1c} cut-off point to 5.9% (41 mmol/mol), the threshold proposed by Hughes et al [12], would lead to improved performance. All analyses were performed using IBM SPSS for Macintosh version 25.0 (IBM Corp., Armonk, NY, USA).

3 Results

There were 900 women who underwent a baseline HbA_{1c}, 31 of whom were excluded from the analysis (Fig. 1). At a mean gestation of 15 ± 2.4 weeks (range 4.3–19.9 weeks), the mean baseline HbA_{1c} was 5.2% (33 mmol/mol) (range 4.3–6.3% (23–45 mmol/mol)), and 12.8% (N = 111) had an HbA_{1c} ≥ 5.7% (39 mmol/mol) of which 4.3% (N = 37) exceeded 5.9% (41 mmol/mol). The maternal and glycemic characteristics of women with an HbA_{1c} of ≥ 5.7% (39 mmol/mol) and < 5.7% (39 mmol/mol) are shown in Table 1. The maternal age, pre-pregnancy BMI, booking BMI, family history of diabetes, fasting and 1-hour post-load glucose levels (before 20 weeks), and GDM diagnosis (before 20 weeks and overall) were significantly higher in the HbA_{1c} ≥ 5.7% (39 mmol/mol) group.

Fig. 1



. Flow diagram of study participants. OGTT = Oral glucose tolerance test; GDM = Gestational diabetes mellitus.

Table 1

Comparison of baseline characteristics between HbA_{1c} categories.

Characteristics	≥5.7% (39 mmol/mol), n = 111		<5.7% (39 mmol/mol), n = 758		*p* value
	n	Mean ± SD or %	n	Mean ± SD or %	
Maternal characteristics					
Age (years)	111	33.13 ± 5.2	758	31.85 ± 5.3	0.02
Pre-pregnancy body mass index (kg/m^2)	110	34.69 ± 4.9	752	33.75 ± 4.4	0.04
Booking body mass index (kg/m^2)	111	35.51 ± 5.0	754	34.39 ± 4.3	0.03
European descent	93/109	85.3	660/757	87.2	0.55
Multiparity	63/109	57.8	367/757	48.5	0.08
Previous GDM	8/73	11.0	40/458	8.7	0.51
Previous macrosomia	21/73	28.8	93/457	20.4	0.12
History of chronic hypertension	15/109	13.8	97/49	13.0	0.76
Previous stillbirth	2/73	2.7	54/458	11.8	0.01
History of congenital malformation	2/73	2.7	17/459	3.7	1.00
Smoking in early pregnancy	13/109	11.9	126/754	16.7	0.26
Alcohol consumption during pregnancy	4/107	3.7	47/750	6.3	0.39
Higher education	60/109	55.0	423/756	56.0	0.92
First-degree family history of diabetes	36	32.4	166	21.9	0.02
History of polycystic ovarian syndrome	12/109	11.0	76/746	10.2	0.74
SBP in early pregnancy (mm Hg)	110	116.6 ± 10.0	754	116.7 ± 10.7	0.88
DBP in early pregnancy (mm Hg)	110	73.7 ± 7.9	754	73.1 ± 8.4	0.47
HDL cholesterol (mmol/L)	107	1.4 ± 0.3	715	1.4 ± 0.3	0.06
LDL Cholesterol (mmo/L)	107	3.1 ± 0.7	716	3.1 ± 0.8	0.52
Triglycerides (mmol/L)	107	1.4 ± 0.5	716	1.4 ± 0.5	0.51
Glycemic characteristics					
OGTT in early pregnancy (<20 weeks)Gestation (weeks)Fasting glucose (mmol/L) 1-hr glucose (mmol/L)2-hr glucose (mmol/L) OGTT in First trimesterGestation (weeks) Fasting glucose (mmol/L)1-hr glucose (mmol/L) 2-hr glucose (mmol/L)OGTT at 13–20 weeksGestation (weeks)Fasting glucose (mmol/L) 1-hr glucose (mmol/L)2-hr glucose (mmol/L)	1111111081072121202090908887	14.8 ± 2.54.8 ± 0.57.5 ± 1.96.3 ± 1.511.3 ± 1.54.9 ± 0.47.5 ± 1.66.0 ± 1.215.6 ± 1.94.8 ± 0.57.6 ± 2.06.3 ± 1.5	7587577117121351351301306236225815 82	15.1 ± 2.44.7 ± 0.57.1 ± 1.76.0 ± 1.311.6 ± 1.44.8 ± 0.57.2 ± 1.86.3 ± 1.315.8 ± 1.84.7 ± 0.57.1 ± 1.76.0 ± 1.3	0.320.0020.010.090.440.300.540.350.370.0040.010.02
OGTT at 24–28 weeksGestation (weeks) Fasting glucose (mmol/L) 1-hr glucose (mmol/L) 2-hr glucose (mmol/L)	57575556	26.3 ± 1.34.5 ± 0.47.9 ± 1.46.2 ± 1.4	466459452447	26.5 ± 1.54.5 ± 0.47.6 ± 1.66.2 ± 1.2	0.400.950.130.84
OGTT at 35–37 weeksGestation (weeks) Fasting glucose (mmol/L)1-hr glucose (mmol/L) 2-hr glucose (mmol/L)	46464141	35.8 ± 0.84.5 ± 0.68.3 ± 1.56.5 ± 1.3	360360347345	35.8 ± 0.94.4 ± 0.47.9 ± 1.46.5 ± 1.2	0.750.690.080.79
GDM prevalence Overall<20 weeks24–28 weeks35–37 weeks	57416/5710/46	51.436.910.521.7	30218469/46749/361	39.824.314.813.6	0.020.0070.550.18
Fasting 110–125 mg/dl (6.1–6.9 mmol/L) First trimester13–20 weeks	0/212/90	0.02.2	3/1355/622	2.20.8	1.000.22
Gestational characteristics					
Gestation at delivery (weeks)	83	40.1 ± 8.0	590	39.5 ± 3.0	0.14
Birth weight (gram)	88	3512.0 ± 542.4	628	3485.5 ± 518.9	0.66

The table shows comparison of maternal, glycaemic, and gestational characteristics between women with higher and lower HbA_{1c} levels. Because there has been considerable interest in the first trimester hyperglycemia, the early OGTT values were further divided into two stages; 0–12 weeks and 13–20 weeks. GDM = Gestational diabetes mellitus; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; HDL = High-density lipoprotein; LDL = Low-density lipoprotein; OGTT = Oral glucose tolerance test.

3.1 Early pregnancy HbA$_{1c}$ and GDM prediction

Table 2 shows the test characteristics of an early pregnancy HbA $_{1c}$ for detecting GDM using the IADPSG criteria. The baseline HbA $_{1c}$ showed a poor area under the ROC curve (AUC) for identifying women with GDM. An HbA $_{1c}$ threshold of 5.7% (39 mmol/mol) showed low sensitivity (15.9%) but high specificity (89.4%) for GDM at any time during pregnancy. Overall, 51.4% of the women in the HbA $_{1c}$ ≥ 5.7% (39 mmol/mol) group developed GDM, and 72% of these cases were detected before 20 weeks (in the < 5.7% (39 mmol/mol) group, this was 61% (184/302) (p = 0.14)). Women with a higher HbA $_{1c}$ in early pregnancy at ≥ 5.7% (39 mmol/mol) had a 1.7 times higher risk for GDM sometime in pregnancy compared to women with an HbA $_{1c}$ of < 5.7% (39 mmol/mol) (adjusted odds ratio (aOR) of 1.72 (1.02–2.89)). The aORs for GDM before 20 weeks, at 24–28 weeks (after excluding early GDM), at 35–37 weeks (after excluding early and 24–28 week GDM) among women in the higher HbA $_{1c}$ group were 2.77 (1.39–5.51), 0.68 (0.26–1.76), and 1.96 (0.84–4.58), respectively. Using fasting glucose of ≥ 6.1 mmol/l (110 mg/dl) in the first trimester gave better ROC characteristics (0.70 (0.53–0.86)) for GDM, but still with poor sensitivity (0% of 3 cases) (Table 2).

Table 2

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Test characteristics of HbA $_{1c}$ at a threshold of ≥ 5.7% (39 mmol/mol) for detecting GDM.

GDM criteria	Gestation	GDM Prevalence (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	AUC (CI), p value *
IADPSG	Throughout gestation	41.3 (359/869)	15.9	89.4	51.4	60.2	0.55 (0.51–0.59), 0.01
	Before 20 weeksFirst trimester13–20 weeks	25.9 (225/869)32.1 (50/156)24.5 (175/713)	18.214.019.4	89.186.889.6	36.933.337.8	75.768.177.4	0.55 (0.50–0.59), 0.04
	24–28 weeks	14.3 (75/524) †(8.6 of total n)	8.0	88.6	10.5	85.2	0.54 (0.47–0.61), 0.27
	35–37 weeks	14.5 (59/407) ‡(6.8 of total n)	16.9	89.7	21.7	86.4	0.57 (0.49–0.65), 0.09
Fasting 6.1–6.9 mmol/l (110–125 mg/dl)	First trimester	1.9 (3/156)	0.0	86.3	0.0	97.8	0.70 (0.53–0.86), 0.24
	13–20 weeks	1.0 (7/712)	28.6	87.5	2.2	99.2	0.69 (0.54–0.83), 0.09

The table shows the test characteristics of early pregnancy HbA $_{1c}$ for detecting GDM at a threshold of ≥ 5.7% (39 mmol/mol). *The area under the receiver operating characteristic curve shows the performance of early pregnancy HbA $_{1c}$ for detecting GDM using all possible HbA $_{1c}$ thresholds; †after excluding early GDM; ‡after excluding early and 24–28 week GDM; GDM = Gestational diabetes mellitus; PPV = Positive predictive value; NPV = Negative predictive value; AUC = Area under the curve; CI = Confidence interval, IADPSG = International Association of Diabetes in Pregnancy Study Groups.

3.2 Early pregnancy HbA$_{1c}$ as a predictor of adverse pregnancy outcomes

There was no significant association between a higher HbA $_{1c}$ ≥ 5.7% (39 mmol/mol) and the risk of adverse pregnancy outcomes (Table 3). In a subgroup analysis stratified by GDM status, women with higher HbA $_{1c}$ in the non-GDM group were less likely to have cesarean section and GWG > 5 kg (Supplemental Table 1). The ROC analysis showed poor performance of HbA $_{1c}$ for predicting adverse pregnancy outcomes regardless of GDM status (Supplemental Table 2).

Table 3

The table layout displayed in this section is not how it will appear in the final version. The representation below is solely purposed for providing corrections to the table. To preview the actual presentation of the table, please view the Proof.

Pregnancy outcomes between HbA $_{1c}$ categories.

Pregnancy outcomes	≥ 5.7% (39 mmol/mol), n = 111 n/N (%)	< 5.7% (39 mmol/mol), n = 758 n/N (%)	p value*	OR (95% CI)	Adjusted OR (95% CI)
Spontaneous abortion	0/88 (0)	2/623 (0.3)	1.00	–	–
Birth weight over 4 kg	15/88 (17.0)	103/628 (16.4)	0.88	1.05 (0.58–1.90)	0.94 (0.46–1.92)
Large for gestational age	12/83 (14.5)	79/566 (14.0)	0.87	1.04 (0.54–2.01)	1.39 (0.64–3.03)
Small for gestational age	3/83 (3.6)	45/568 (7.9)	0.26	0.44 (0.13–1.44)	0.82 (0.22–3.09)
Preeclampsia	3/82 (3.7)	18/554 (3.2)	0.74	1.13 (0.32–3.93)	0.77 (0.15–3.82)
Pregnancy induced hypertension	7/82 (8.5)	69/552 (12.5)	0.37	0.65 (0.29–1.48)	0.44 (0.15–1.27)
Preterm birth	6/83 (7.2)	26/586 (4.4)	0.27	1.68 (0.67–4.21)	1.57 (0.48–5.21)
Caesarean section	29/88 (33.0)	233/622 (37.5)	0.48	0.82 (0.51–1.32)	0.55 (0.30–1.00)
Hyperbilirubinemia	7/81 (8.6)	21/515 (4.1)	0.09	2.23 (0.91–5.42)	1.56 (0.55–4.41)
Neonatal Intensive Care Unit stay	6/76 (7.9)	47/509 (9.2)	0.83	0.84 (0.35–2.04)	0.64 (0.23–1.78)
Weight gain under 5 kg	22/65 (33.8)	121/498 (24.3)	0.10	1.59 (0.92–2.77)	1.35 (0.72–2.52)
Induction of labour	37/82 (45.1)	281/553 (50.8)	0.35	080 (0.50–1.27)	0.81 (0.45–1.46)

The table shows ORs (adjusted and unadjusted) for the development of adverse pregnancy outcomes among women with an early pregnancy HbA $_{1c}$ of ≥ 5.7% (39 mmol/mol) compared to those with an HbA1c of < 5.7% (39 mmol/mol). Results were adjusted for maternal age, pre-pregnancy body mass index, booking body mass index, family history of diabetes, country, randomisation group, GDM status and GDM treatment. *p value of the Fisher's Exact test; –not applicable due to small numbers; GDM = Gestational diabetes mellitus; OR = Odds ratio; CI = Confidence interval.

In the sensitivity analysis, an HbA $_{1c}$ threshold of 5.9% (41 mmol/mol) showed a small increase in specificity with a decrease in sensitivity for detecting GDM (Supplemental Table 3). An HbA $_{1c}$ ≥ 5.9% (41 mmol/mol) did not predict adverse pregnancy outcomes (Supplemental Table 4).

4 Discussion

Our study of overweight and obese women from a largely European background shows that while GDM was present in 36.9% of women with an HbA $_{1c}$ ≥ 5.7% (39 mmol/mol) before 20 weeks of gestation, this was also the case in 24.3% of the remaining women, a numerically much larger group. Our results clearly show the poor sensitivity of an early pregnancy HbA $_{1c}$ for detecting GDM. While the 5.7% (39 mmol/mol) cut-off was highly specific for GDM, this threshold could not correctly identify most of the cases of GDM with a false negative rate of 81.8% before 20 weeks and 84.1% for GDM at any time. Low ROC AUC values show the poor ability of the HbA $_{1c}$ to detect GDM at any time regardless of the week of pregnancy. This low sensitivity was also shown by Hughes et al. [12] (18.8% for the threshold of ≥ 5.9% for early GDM) using New Zealand criteria, and Odsaeter et al. [20] (0% sensitivity for the threshold of 5.8% (40 mmol/mol) after 18 weeks' gestation) using modified IADPSG criteria. Several other studies also reported poor sensitivity of early HbA $_{1c}$ for diagnosing GDM in late pregnancy, with the value ranging between 0.9% and 25.7% for a higher threshold above ≥ 5.7–5.9% (39–41 mmol/mol) [11,13,20–22]. The AUC values in our results were similar to those reported in other studies with poor values at different pregnancy weeks and throughout gestation [20–23].

In our study, women with an HbA $_{1c}$ of ≥ 5.7% (39 mmol/mol) were not at increased risk of adverse pregnancy outcomes. Among those with negative OGTT results using IADPSG criteria, there was no relationship between adverse pregnancy outcomes and the higher HbA $_{1c}$ except that women with higher values had less GWG and cesarean rate (possibly from lifestyle interventions). Several previous studies have shown mixed results. Similar to our findings, Fong et al. [10] and Osmundson et al. [11] found no adverse outcomes associated with higher HbA $_{1c}$ ≥ 5.7% (39 mmol/mol). In contrast, a study by Hughes et al. [12] reported a strong relationship between higher HbA $_{1c}$ values (≥5.9% (41 mmol/mol)) and adverse pregnancy outcomes such as preeclampsia, perinatal death, major congenital anomaly, and shoulder dystocia, but not LGA (customized) or macrosomia. The difference in ability to predict pregnancy outcomes in our study compared with the Hughes et al. study may be due to several factors including sample size and ethnic differences (the Hughes et al. study had a large number of Polynesian women with a higher HbA $_{1c}$), and perhaps using the New Zealand criteria, a large number of women with IADPSG-defined GDM remained undiagnosed and untreated but in the "non-GDM" analyses. Similarly, Mane et al.[13] found a higher risk of preeclampsia and macrosomia among participants with a higher HbA $_{1c}$ in a multiethnic cohort using the National Diabetes Data Group (NDDG) OGTT criteria following a 50 g glucose challenge test. In contrast, two other studies [20,23] found no association between early HbA $_{1c}$ values and outcome variables such as preeclampsia, birthweight, macrosomia, polyhydramnios, SGA, and hypertensive disorders. A direct comparison between previous studies was difficult as their population characteristics and sample sizes differed substantially. Also, there was variability in the criteria adopted for GDM diagnosis (those adopted included IADPSG criteria [10,11,21,23], World Health Organization (WHO) 1999 criteria [20], Modified IADPSG criteria [20], National Diabetes Data Group (NDDG) criteria [22], and Carpenter-Coustan (CC) criteria [10]).

Our data question the use of an early HbA $_{1c}$ for detecting/predicting hyperglycemia below the cut point for diabetes in pregnancy. Based on our findings, we suggest that at these low levels, accuracy is severely influenced by the variability between individuals including red blood cell (RBC) longevity and ethnicity. The longer a RBC survives, the longer time there is for glycation, even with a normal blood glucose level. This non-glycaemic influence reduces the discriminative power of HbA $_{1c}$ for detecting mild hyperglycemia as evidenced by low AUC values for GDM defined by the IADPSG criteria. The discordance in association between higher HbA $_{1c}$ and GDM-associated adverse outcomes, is most likely due to the impact of GDM treatment/lifestyle intervention and overall glycemia, being less than the influence of inter-individual variation in the mean RBC age across the population. The differential effect of turnover on HbA $_{1c}$, reproducible individuals, has been shown outside of pregnancy [24,25]. On the other hand, the contribution of variability in mean RBC age to the HbA $_{1c}$ level appears to be less at higher levels of glycemia. This is evident from the higher AUC for detecting GDM defined by the higher fasting glucose of ≥ 6.1 mmol/l (110 mg/dl).

We, therefore, suggest that an early pregnancy HbA $_{1c}$ value should not be used as a biomarker for detecting mild hyperglycemia in pregnancy and that a threshold of ≥ 5·7% (39 mmol/mol) has limited utility in the prediction of poor pregnancy outcomes in obese pregnant women. Further studies are urgently needed to define the best strategies to diagnose and identify early GDM.

A major limitation of our study was the high percentage of missing data (17.6–32.7% for the majority of the outcome variables) which may have influenced our study findings. Secondly. In the higher HbA $_{1c}$ group, 8.8% of the women diagnosed with GDM received medication therapy and 57% of the non-GDM women (excluding women in the usual care, placebo, and vitamin D limbs) received some kind of lifestyle intervention (Supplemental Table 5). This may have affected the outcome of the pregnancy and attenuated the effects of higher HbA $_{1c}$ on adverse outcomes. Nevertheless, the analyses have been adjusted for lifestyle intervention and GDM treatment, and this made no difference to the results. Furthermore, in spite of the clinical treatment, pregnancy outcomes were still worse among women with GDM. We have previously shown that neither gestational weight gain limitation across the cohort, lifestyle change nor Vitamin D supplementation has a substantive impact on pregnancy outcomes or GDM incidence [17,18]. Further, the IADPSG criteria were developed for diagnosis of GDM at 24–28 weeks' gestation, not early pregnancy, and criteria for this time point are under active investigation [26,27]. Moreover, our participants were mainly overweight/obese European women (87%), which limits the generalizability of the study results. Also, all the women had accepted to participate in a life-style intervention study, and therefore these women might not be representative of an unselected population Finally, full blood count data were not available for the identification of possible shorter or longer red blood cell longevity, so results were not adjusted for the presence of anaemia.

In conclusion, an early HbA $_{1c}$ measurement was not useful in the prediction of GDM in obese European women. An HbA $_{1c}$ with a threshold of 5.7% (39 mmol/mol) is a specific but insensitive biomarker for GDM and is not associated with adverse pregnancy outcomes. Because of the "dilution" effect of hemoglobin glycation by RBC turnover variation at these relatively low levels of HbA $_{1c}$, the proposed threshold has limited utility in screening for early GDM, in spite of its value for detecting diabetes in pregnancy. Future studies are needed to confirm the results in different populations.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Author Contributions

JI undertook the statistical analyses, interpreted the data and drafted the manuscript. DS conceived the project, supervised JI, interpreted the data, reviewed and edited the draft and provided critical input to the manuscript. DS, RC, RD, AVA, AL, EW, AK, FD, PD, ERM, DH and FS designed and executed the DALI study and provided input for the interpretation of the results. DS was the study coordinator. JMA, SG, MGD, AB, JH, AZ, DMJ, LTA, HS, JJ contributed to the execution of the study and provided input for the interpretation of the results. GD designed and executed the study and provided input for the interpretation of the results. He was the principal investigator of the study. MVP designed and executed the study and provided input for the interpretation of the results. She was the sponsor of the study. All authors read and approved the final manuscript. J.I. is the guarantor of this work and takes full responsibility for the contents of this article.

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Appendix A Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108378.

References

The corrections made in this section will be reviewed and approved by a journal production editor. The newly added/removed references and its citations will be reordered and rearranged by the production team.

[1] Leng J., Shao P., Zhang C., et al. Prevalence of gestational diabetes mellitus and its risk factors in Chinese pregnant women: a prospective population-based study in Tianjin. China. PLoS One 2015;10. doi:10.1371/journal.pone.0121029. e0121029.

[2] Lavery J.A., Friedman A.M., Keyes K.M., Wright J.D., Ananth C.V. Gestational diabetes in the United States: temporal changes in prevalence rates between 1979 and 2010. BJOG 2017;124:804–813. doi:10.1111/1471-0528.14236.

[3] Djelmis J., Pavic M., Mulliqi Kotori V., Pavlic Renar I., Ivanisevic M., Oreskovic S. Prevalence of gestational diabetes mellitus according to IADPSG and NICE criteria. Int J Gynaecol Obstet 2016;135:250–254. doi:10.1016/j.ijgo.2016.07.005.

[4] American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019;42:S13–28. https://doi.org/10.2337/dc19-S002.

[5] Gallagher E.J., Le Roith D., Bloomgarden Z. Review of hemoglobin A(1c) in the management of diabetes. J Diabtes 2009;1:9–17. doi:10.1111/j.1753-0407.2009.00009.x.

[6] O'Connor C., O'Shea P.M., Owens L.A., Carmody L., Avalos G., Nestor L., et al. Trimester-specific reference intervals for haemoglobin A1c (HbA1c) in pregnancy. Clin Chem Lab Med 2011;50:905–909. doi:10.1515/cclm.2011.397.

[7] Mills J.L., Jovanovic L., Knopp R., et al. Physiological reduction in fasting plasma glucose concentration in the first trimester of normal pregnancy: the diabetes in early pregnancy study. Metabolism 1998;47(1140–4). 10.1016/S0026-0495(98)90290–6.

[8] Lurie S., Mamet Y. Red blood cell survival and kinetics during pregnancy. European J Obstet Gynecol Reprod Bio 2000;93:185–192. doi:10.1016/S0301-2115(00)00290-6.

[9] Hartland A.J., Smith J.M., Clark P.M.S., Webber J., Chowdhury T., Dunne F. Establishing trimester- and ethnic group-related reference ranges for fructosamine and HbA1c in non-diabetic pregnant women. Ann Clin Biochem 1999;36:235–237. doi:10.1177/000456329903600218.

[10] Fong A., Serra A.E., Gabby L., Wing D.A., Berkowitz K.M. Use of hemoglobin A1c as an early predictor of gestational diabetes mellitus. Am J Obstet Gynecol 2014;211(641):e1–e7. doi:10.1016/j.ajog.2014.06.016.

[11] Osmundson S.S., Zhao B.S., Kunz L., et al. First trimester hemoglobin A1c prediction of gestational diabetes. Am J Perinatol 2016;33:977–982. doi:10.1055/s-0036-1581055.

[12] Hughes R.C., Moore M.P., Gullam J.E., Mohamed K., Rowan J. An early pregnancy HbA1c >/=41 mmol/mol (5.9%)is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. Diabetes Care 2014;37:2953–2959. doi:10.2337/dc14-1312.

[13] Mañé L., Flores-Le Roux J.A., Benaiges D., et al. Role of First-Trimester HbA1c as a Predictor of Adverse Obstetric Outcomes in a Multiethnic Cohort. J Clin Endocrinol Metab 2017;102:390–397. doi:10.1210/jc.2016-2581.

[14] Ministry of Health. 2014. Screening, Diagnosis and Management of Gestational Diabetes in New Zealand: A clinical practice guideline. Wellington: Ministry of Health. Available from https://www.health.govt.nz/publication/screening-diagnosis-and-management-gestational-diabetes-new-zealand-clinical-practice-guideline. Accessed January 29, 2019.

[15] Jelsma J.G., van Poppel M.N., Galjaard S., et al. DALI: Vitamin D and lifestyle intervention for gestational diabetes mellitus (GDM) prevention: an European multicentre, randomised trial-study protocol. BMC pregnancy and childbirth 2013;13:142. doi:10.1186/1471-2393-13-142.

[16] Metzger B.E., Gabbe S.G., Persson B., et al. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care 2010;33:676–682. doi:10.2337/dc09-1848.

[17] Simmons D., Devlieger R., Van Assche A., et al. Effect of physical activity and/or healthy eating on GDM risk: the DALI lifestyle study. J Clin Endocrinol Metab 2017;102:903–913. doi:10.1210/jc.2016-3455.

[18] Corcoy R., Mendoza L.C., Simmons D., et al. The DALI vitamin D randomized controlled trial for gestational diabetes mellitus prevention: No major benefit shown besides vitamin D sufficiency. Clin Nutr (in press) 2019. doi:10.1016/j.clnu.2019.04.006.

[19] Immanuel J., Simmons D. Screening and treatment for early-onset gestational diabetes mellitus: a systematic review and meta-analysis. Curr Diab Rep 2017;17:115. doi:10.1007/s11892-017-0943-7.

[20] Odsæter I.H., Åsberg A., Vanky E., et al. Hemoglobin A1c as screening for gestational diabetes mellitus in Nordic Caucasian women. Diabetol Metab Syndr 2016;8:43. doi:10.1186/s13098-016-0168-y.

[21] Wu K., Cheng Y., Li T., et al. The utility of HbA1c combined with haematocrit for early screening of gestational diabetes mellitus. Diabetol Metab Syndr 2018;10:14. doi:10.1186/s13098-018-0314-9.

[22] Benaiges D., Flores-Le Roux J.A., Marcelo I., et al. Is first-trimester HbA1c useful in the diagnosis of gestational diabetes?. Diabetes Res Clin Pract 2017;133:85–91. doi:10.1016/j.diabres.2017.08.019.

[23] Amylidi S., Mosimann B., Stettler C., Fiedler G.M., Surbek D., Raio L. First-trimester glycosylated hemoglobin in women at high risk for gestational diabetes. Acta Obstet Gynecol Scand 2016;95:93–97. doi:10.1111/aogs.12784.

[24] Cohen R.M., Franco R.S., Smith E.P., Higgins J.M. When HbA1c and blood glucose do not match: How much is determined by race, by genetics, by differences in mean red blood cell age?. J Clin Endocrinol Metab 2019;104:707–710. doi:10.1210/jc.2018-02409.

[25] Cohen R.M., Franco R.S., Khera P.K., et al. Red cell life span heterogeneity in hematologically normal people is sufficient to alter HbA1c. Blood 2008;112:4284–4291. doi:10.1182/blood-2008-04-154112.

[26] Wexler D.J., Powe C.E., Barbour L.A., et al. Research gaps in gestational diabetes mellitus: executive summary of a national institute of diabetes and digestive kidney disease workshop. Obstet Gynecol 2018;132:496–505. doi:10.1097/AOG.0000000000002726.

[27] Simmons D., Hague W.M., Teede H.J., et al. Hyperglycemia in early pregnancy: the treatment of booking gestational diabetes mellitus (TOBOGM) study. A randomized controlled trial. Med J Aust 2018;209(405–6). doi:10.5694/mja17.01129.

Highlights

- Early pregnancy HbA1c is a poor predictor of gestational diabetes.
- An HbA $_{1c}$ ≥ 5.7% (39 mmol/mol) has poor sensitivity for GDM regardless of gestation.
- An HbA $_{1c}$ ≥ 5.7% (39 mmol/mol) was not associated with greater risk of adverse outcomes.

Appendix A Supplementary material

The following are the Supplementary data to this article:

Multimedia Component 1

Supplementary data 1

Queries and Answers

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