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HbA1c during early pregnancy reflects beta-cell dysfunction in women developing GDM

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ABSTRACT

Introduction It is of current interest to assess eligibility of hemoglobin A1c (HbA1c) as a screening tool for earlier identification of women with risk for more severe hyperglycemia in pregnancy but data regarding accuracy are controversial. We aimed to evaluate if HbA1c mirrors pathophysiological precursors of glucose intolerance in early pregnancy that characterize women who develop gestational diabetes mellitus (GDM).

Research design and methods 220 pregnant women underwent an HbA1c measurement as well as an oral glucose tolerance test (OGTT) with multiple measurements of glucose, insulin and C-peptide for evaluation of insulin sensitivity and beta-cell function at 16th gestational week (IQR: 14–18). Clinical follow-ups were performed until end of pregnancy.

Results Increased maternal HbA1c ≥5.7% (39 mmol/mol) corresponding to pre-diabetes outside of pregnancy was associated with altered glucose dynamics during the OGTT. Pregnancies with early HbA1c ≥5.7% showed higher fasting (90.4±13.2 vs 79.7±7.2 mg/dL, p<0.001), mean (145.6±31.4 vs 116.2±21.4 mg/dL, p<0.001) as well as maximum glucose concentrations and tended to a delay in reaching the maximum glucose level compared with those with normal-range HbA1c (186.5±42.6 vs 147.8±30.1 mg/dL, p<0.001). Women with increased HbA1c showed impaired beta-cell function and differences in disposition index independent of body mass index status. We observed a high specificity for the HbA1c cut-off of 5.7% for GDM manifestation (0.96, 95% CI 0.91 to 0.98) or need of glucose-lowering medication (0.95, 95% CI 0.90 to 0.98) although overall predictive accuracy was moderate to fair. Further, elevated HbA1c was associated with higher risk for delivering large-for-gestational-age infants, also after adjustment for GDM status (OR 4.4, 95% CI 1.2 to 15.0, p=0.018).

Conclusions HbA1c measured before recommended routine screening period reflects early pathophysiological derangements in beta-cell function and glucose disposal that are characteristic of GDM development and may be useful in early risk stratification.

Significance of this study

What is already known about this subject?

- Several studies reported that women with elevated HbA1c during early pregnancy have a higher risk for gestational diabetes mellitus (GDM) manifestation and/or adverse pregnancy outcomes.

What are the new findings?

- Increased HbA1c ≥5.7 measured during early pregnancy reflects impairments in beta-cell function and glucose disposal that are characteristic of GDM. Pregnant women with elevated HbA1c showed higher glucose levels during oral glucose tolerance test as well as alterations in dynamics.
- Although predictive accuracy of HbA1c was moderate to fair, we observed a high specificity for the HbA1c cut-off of 5.7% for GDM manifestation or need of glucose-lowering medication.
- Risk for large for gestational age was higher in women with elevated HbA1c at early pregnancy even after adjustment for GDM status.

How might these results change the focus of research or clinical practice?

- These associations on pathophysiological level argue for the utility of HbA1c as early predictor for pregnancies at glucometabolic risk that may profit from earlier interventional strategies.

INTRODUCTION

Gestational diabetes confers mother and offspring to perinatal and postnatal consequences that are primarily related to degree of maternal hyperglycemia.[1] Actually, routine diagnostic testing by glucose challenge or tolerance tests is broadly applied during 24th–28th gestational weeks (GW). However, maternal dysglycemia develops earlier to diagnosis and by crossing the placenta in greater quantities, glucose as a substrate induces fetal overgrowth.[1] Considering the delay of first clinical contact after laboratory testing as well as time for instruction of self-glucose measurements and implementation of dietary measures considerable time passes where the fetus is exposed to excess intrauterine hyperglycemia. In more severe cases of gestational diabetes mellitus (GDM) this could have detrimental consequences because time for intensive interventions gets limited.

Various organizations recommend an early screening for glucometabolic disorders during pregnancy but there is no consistent GDM strategy. This condition is already emphasized as it was recently outlined that controversies will remain as long as profound scientific evidence is lacking.[2 3] A universal implementation of a strategy would require a simple but effective tool for risk stratification that identifies relevant glucose intolerance with imminent threat for fetal and pregnancy outcome as early as possible—but without elevating associated costs and this is quite challenging. The actual pandemic situation due to the COVID-19 outbreak demonstrates impressively the relevance of fast, reliable and simple parameters that enable appropriate adaptations of diagnostic strategies when access to healthcare services is limited. In this context hemoglobin A1c (HbA1c) gains interest as for its practicability and convenience in clinical practice. Further HbA1c gives an estimate of average glucose over the prior 3 months, why guidelines recommend to set an HbA1c of 6.5% during first trimester as a threshold for unrecognized pre-existing diabetes.[4 5] However, risk for perinatal complications increases in proportion to elevation in maternal HbA1c.[6] Thus, an HbA1c range below 6.5% but corresponding to pre-diabetes in non-pregnant state might also have some merit in identifying women with enhanced risk for perinatal complications related to maternal glucose deterioration already during early pregnancy. Against expectation only a few studies focused on HbA1c for evaluation of baseline glycemic situation before regular screening period in second/third trimester. Most recently, data from a case–control study showed a linear association of HbA1c level and GDM development such that women with 5.7% HbA1c had an almost three times elevated GDM risk.[7] Moreover, longitudinal measurements throughout pregnancy remained different between women with GDM and controls.[7] But before arguing about clinical reliability it is indicated to further characterize the contribution of HbA1c to prediction of GDM by a more detailed evaluation of pathophysiological associations. In this matter, it could be of interest how well HbA1c reflects glucose deterioration and correlates to severity of insulin resistance or beta-cell dysfunction during early gestation.

Thus, we sought to examine the relation of HbA1c to concomitant status of insulin sensitivity and beta-cell function at early pregnancy and to evaluate its accuracy for prediction of GDM manifestation. Further, we evaluated if early maternal HbA1c is independently associated with neonatal birth weight and risk for delivery of large-for-gestational-age (LGA) infants.

RESEARCH DESIGN AND METHODS

Study population

This prospective longitudinal study was performed at the Division of Endocrinology and Metabolism, Department of Internal Medicine III, Medical University of Vienna between 2010 and 2014 as previously reported in.[8] Participants were recruited among all pregnant women at ≤21st GW, who were referred to our diabetes and pregnancy outpatient clinics in the framework of a tertiary care center. After screening for exclusion criteria (ie, presence of chronic or serious acute infections, hematological diseases or diseases of the hematopoietic system, severely impaired liver or kidney function or infectious diseases) remaining eligible women were asked for consent and were enrolled for further study examinations (visit 1). A total of 223 women underwent further clinical evaluations until delivery at 24th–28th GWs (visit 2), 30th–34th GWs (visit 3) and >36th GW (visit 4). A flow chart describing our study population is given in online supplemental figure S1.

Clinical examinations and follow-ups

At initial assignment all participants were characterized by a broad risk evaluation comprising body mass index (BMI) (preconceptional and actual) and medical history. Subsequently, a 2-hour oral glucose tolerance test (OGTT) was performed at visit 1 (median: 16 weeks, IQR: 14–18) after a 10–12 hours overnight fast with glucose, insulin and C-peptide determination after venous blood collection at fasting and after 30, 60, 90 and 120 min following a 75 g glucose load. Whereas those with OGTT results diagnostic for GDM were immediately assigned for therapeutic regimens, participants with negative OGTT result were clinically examined and repeated OGTT examination at recommended period of 24th–28th weeks (visit 2) to ascertain diagnosis.[5] Thresholds for diagnosis of GDM were defined by a fasting plasma glucose level of ≥92 mg/dL (but <126 mg/dL), a 1-hour glucose level of ≥180 mg/dL or a 2-hour glucose level of ≥153 mg/dL after glucose load and were applied at first examination in early pregnancy as well as at visit 2.

At first antenatal visit four women were classified as having pre-existing diabetes by elevated fasting plasma glucose ≥126 mg/dL and/or HbA1c ≥6.5% (47.54 mmol/mol) in accordance with the International Association of Diabetes and Pregnancy Study Groups (IADPSG) guidelines[5] and hence were not eligible for further participation.

Moreover, six women were treated by insulin therapy during later follow-up due to incident macrosomia and elevated fasting glucose and thus were considered as having GDM. Altogether, GDM diagnosis was established primarily by OGTT results according to the IADPSG criteria[5] or clinical indication of insulin therapy. Analysis of differences in baseline OGTT-derived parameters was previously reported.[8]

Laboratory measurements

All parameters were measured according to the international standard laboratory methods at our certified Department of Medical and Chemical Laboratory Diagnostics (http://www.kimcl.at/). HbA1c was measured at each visit by the technique of high-performance liquid chromatography using Variant II, Bio-Rad,

International Federation of Clinical Chemistry (IFCC)-standardized and Diabetes Control and Complications Trial (DCCT)-aligned coefficient of variation (CV)=1.8% (HbA1c=5.6%). Glucose, insulin and C-peptide were determined from venous blood samples obtained during the OGTT examinations as well as at each further visit, where a venous blood sample was obtained at fasting condition. Plasma glucose concentrations were measured by the hexokinase method with a CV of 1.3%. Insulin (CV: 4%–7%) and C-peptide (CV: 3%–4%) were measured by chemiluminescence immune assays.

Calculations

Total body insulin sensitivity from dynamic OGTT measures of glucose and insulin was assessed by the composite index (ISI-comp, dimensionless),[9] in addition to the quantitative insulin sensitivity check index (dimensionless),[10] representing an approximate of hepatic insulin resistance. Insulin secretion was assessed by using modified insulinogenic indices to describe early (Sec-early, Δinsulin/Δglucose 0–30 min, µU/mg), late (Sec-late, area under the curve (AUC)-insulin/AUC-glucose 60–120 min, µU/mg) and total insulin response to glucose challenge (Sec-total, AUC-insulin/AUC-glucose 0–120 min, µU/mg).[11 12] The oral disposition index (ISSI-2, dimensionless) was calculated as the product of ISI-comp and total insulin secretion to reflect the ability of beta cells to adapt to impaired insulin action. The respective AUCs of glucose, insulin and C-peptide during the OGTT were calculated by using the trapezoidal rule.

Neonatal care and anthropometric measures

Neonatal birth weight was determined by a calibrated scale. Birth length was measured to the nearest 0.1 cm by using an infant board with a stadiometer. Age and sex-adjusted percentiles were estimated by applying international anthropometric standards, that is, the INTERGROWTH-21st standards.[13]

Statistical analysis

Categorical variables were summarized by counts and percentages and compared by Pearson's χ^2 test. Continuous variables were summarized by mean±SD as well as median and IQR, respectively. Comparisons of continuous parameters between three groups were performed by Student's t-test and the Wilcoxon rank-sum test (and the Brunner-Munzel test as a supporting approach) was used in case of skewed distributed parameters. An adjustment for covariates such as BMI was performed by analysis of covariance and the proportional odds cumulative logit model, respectively. Binary logistic regression was used to evaluate the association between continuous variables and dichotomous outcomes (eg, GDM manifestation or GDM with need of pharmacotherapy). Thereby, the predictive accuracy of these parameters was assessed by the area under the receiver operating characteristic curves (ROC-AUC). Moreover, statistical performance measures including sensitivity, specificity and predictive values as well as their 95% CIs are provided as appropriate. Statistical analysis was performed with R (V.3.5.3) and contributed packages.[14] The two-sided significance level was set to 0.05. However, p values were interpreted in an explorative manner and there was no further adjustment for multiplicity as not otherwise indicated.

RESULTS

Descriptive characteristics of the study sample are provided in table 1. Elevated HbA1c was associated with higher pregestational and early pregnancy BMI levels as well as altered glucose dynamics during the OGTT performed at first or early second trimester. Thereby, the subgroup with elevated HbA1c ≥5.7 showed higher fasting, mean as well as maximum glucose concentrations compared with those with HbA1c in normal range (186.5±42.6 vs 147.8±30.1 mg/dL, p<0.001) during this test as visualized in figure 1. Moreover, the subgroup with elevated HbA1c tended to delay in reaching the maximum concentrations of glucose (p<0.001). Whereas no differences were observed for insulin action either assessed from fasting or dynamic measures, patients with elevated HbA1c showed a notable decrease in early and total insulin secretion, resulting in altered beta-cell function (figure 2A–D). The observed differences in insulin secretion and the ISSI-2 remained constant after controlling for early pregnancy BMI and pregestational BMI, respectively. Furthermore, HbA1c values were associated with the risk for GDM or requirement of insulin during pregnancy. Logistic regression revealed that the predictive accuracy of HbA1c (in terms of ROC-AUC) was moderate to fair and comparable to pregestational BMI (67.0%) as presented in figure 3. The combination of HbA1c and BMI increased the predictive performance (ROC-AUC) to 72.4%. However, we observed a high specificity for the HbA1c cut-off of 5.7% (39 mmol/mol) for GDM manifestation (0.96, 95% CI 0.91 to 0.98) or need of glucose-lowering medication (0.95, 95% CI 0.90 to 0.98). Details of performance measures are provided in table 2. In addition, patients with early elevated HbA1c showed a higher risk for delivering LGA infants (OR 4.2, 95% CI 1.2 to 13.0, p=0.016) even after adjustment for GDM status (OR 4.4, 95% CI 1.2 to 15.0, p=0.018).

CONCLUSIONS

In our study we observed that increased HbA1c ≥5.7 measured during early pregnancy reflects impairments in beta-cell function and glucose disposal that are characteristic of GDM. Further, HbA1c at early pregnancy may be useful as an indicator of disturbed beta-cell function even independent of BMI. As far as we know, this is the first study providing data of simultaneously performed 75 g OGTT including insulin and C-peptide measurements in addition to HbA1c during early pregnancy. In our population, increased maternal HbA1c was associated with higher glucose levels during OGTT as well as alterations in dynamics. Moreover, analysis of OGTT-derived indices

Table 1 Characteristics of the study sample and glucometabolic parameters

	n	HbA1c <5.7	n	HbA1c ≥5.7	P value
Age (years)	197	31.9±5.2	23	33.4±5.1	0.191
Week of gestation	197	15.9±2.9	23	15.2±3.2	0.242
Early pregnancy BMI (kg/m²)	197	28.0±5.7	23	32.2±5.6	<0.001
Pre-pregnancy BMI (kg/m²)	196	26.5±5.8	23	30.5±5.4	0.002
GDM	197	67 (34.0%)	23	17 (73.9)	<0.001
IGDM	197	44 (22.3%)	23	15 (65.2%)	<0.001
Fasting glucose (mg/dL)	196	79.7±7.2	23	90.4±13.2	<0.001
60 min post-OGTT glucose (mg/dL)	196	138.9±34.6	23	182.6±44.3	<0.001
120 min post-OGTT glucose (mg/dL)	196	106.0±26.8	23	131.3±32.3	<0.001
Mean glucose (mg/dL)	180	116.2±21.4	22	145.6±31.4	<0.001
Maximum glucose (mg/dL)	180	147.8±30.1	22	186.5±42.6	<0.001
Fasting insulin (µU/mL)	196	4.38 (1.90–8.51)	23	3.71 (2.31–9.09)	0.709
Mean insulin (µU/mL)	178	39.9 (28.8–62.7)	22	40.7 (26.1–62.8)	0.901
Fasting C-peptide (ng/mL)	195	1.40 (1.10–2.00)	23	1.80 (1.45–2.70)	0.010
Mean C-peptide (ng/mL)	178	6.63 (5.33–8.20)	22	7.26 (5.91–9.27)	0.158
Early insulin secretion (µU/mg)	187	76.9 (48.7–122.5)	22	39.5 (24.2–73.4)	0.001
Late insulin secretion (µU/mg)	177	43.5 (31.0–65.1)	22	38.8 (25.8–52.9)	0.108
Total insulin secretion (µU/mg)	177	38.4 (26.1–57.0)	22	29.6 (21.9–42.2)	1960.039
QUICKI (dimensionless)	195	0.40±0.05	22	0.39±0.05	0.362
ISI-comp (dimensionless)	170	9.27±5.63	22	7.86±5.22	0.265
ISSI-2 (dimensionless)	170	319±128	22	213±129	<0.001

Data are mean±SD, median (IQR) or counts and percentages for patients with normal and elevated HbA1c at early pregnancy.
BMI, body mass index; GDM, gestational diabetes mellitus; HbA1c, hemoglobin A1c; IGDM, insulin-treated gestational diabetes mellitus; ISI-comp, composite index; ISSI-2, oral disposition index; OGTT, oral glucose tolerance test; QUICKI, quantitative insulin sensitivity check index.

showed impaired beta-cell function and differences in disposition index in women with increased HbA1c which were independent of early pregnancy BMI or pregestational BMI status.

Characteristic of GDM is the insufficient compensation of increasing insulin requirements during pregnancy primarily due to defective beta-cell function.[1 15] Concomitant to changes in the insulin signaling cascade, the growing placenta produces hormones with insulin-desensitizing effects that increase insulin resistance—here maternal adiposity gains relevance as an antecedent risk factor during early pregnancy that defines level of basal insulin sensitivity.[1 16] To sum up, maintenance of euglycemia during gestation depends mainly on the plasticity of maternal beta-cell function to sufficiently compensate insulin resistance, which aggravates depending on additional metabolic risk factors

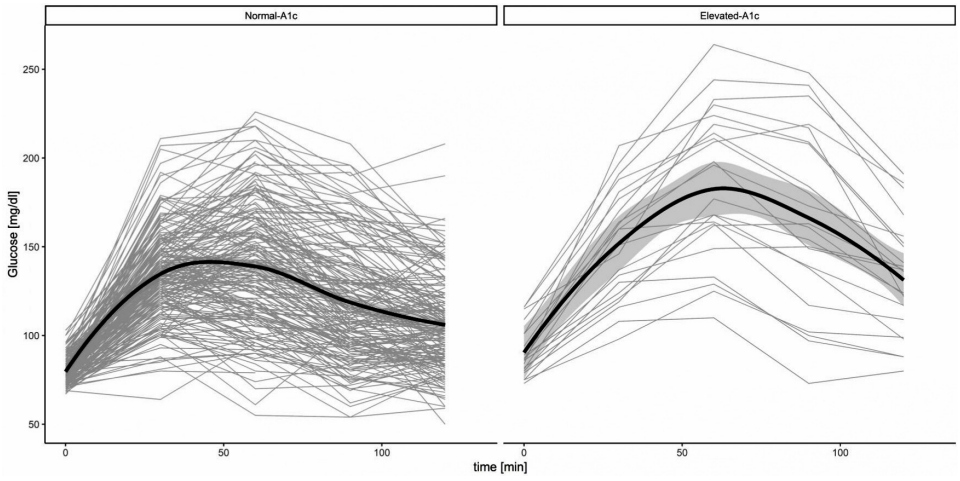

Figure 1 Spaghetti plots of plasma glucose dynamics during a 2-hour oral glucose tolerance test (OGTT) in pregnant women with normal (<5.7%) and elevated (≥5.7) HbA1c levels at early gestation. The solid line represents the weighted mean value and the gray area represents the 95% CI. HbA1c, hemoglobin A1c.

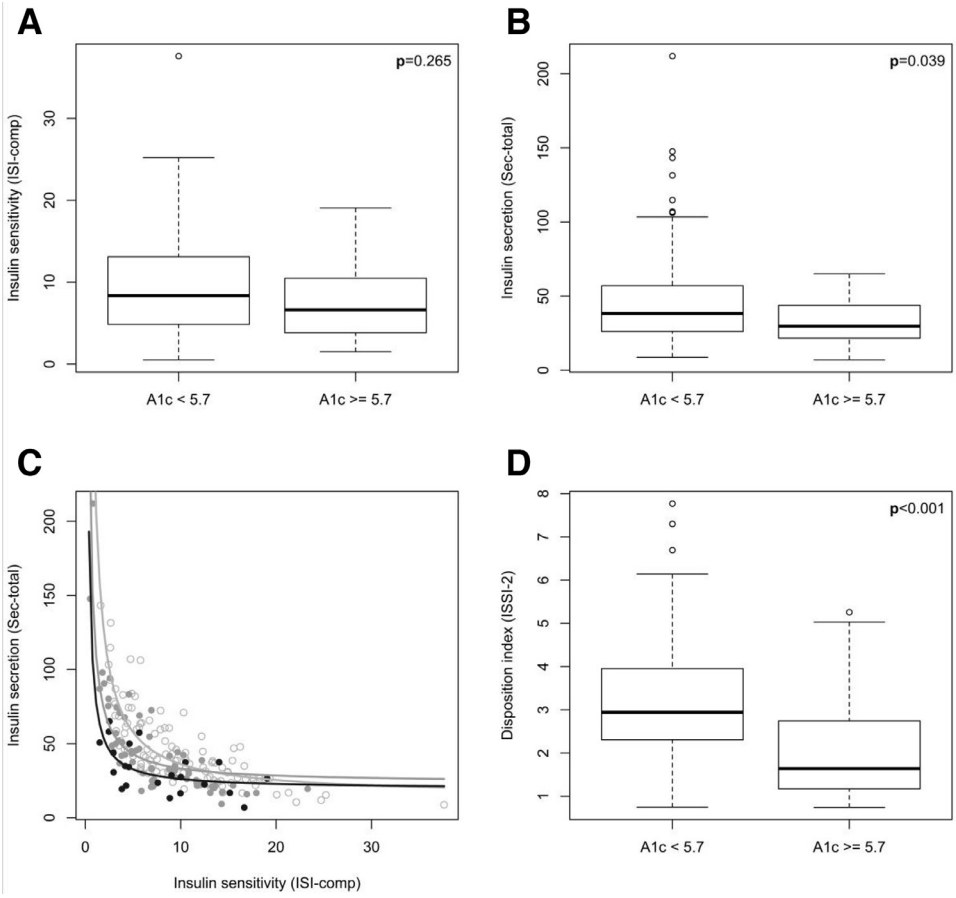

Figure 2 Box-whisker plots representing comparisons of insulin sensitivity (A) and insulin secretion (B) from the oral glucose tolerance test (OGTT), the association between insulin sensitivity and insulin secretion and the estimated hyperbolic regression line for normal glucose-tolerant controls (light gray) as well as women with gestational diabetes mellitus (GDM) and normal HbA1c (dark gray) and women with elevated HbA1c (black) (C) as well as the disposition index, representing beta-cell function (D). HbA1c, hemoglobin A1c.

during pregnancy—otherwise it is a matter of time that GDM becomes evident.[1 15] However, measures indicating beta-cell function or the disposition index require too extensive and precise procedures including multiple blood samples and thus are inconvenient for first trimester screening. HbA1c during early pregnancy may give an estimate of the maternal glucose metabolism at baseline before significant hormonal pregnancy-related changes develop—thus it offers an

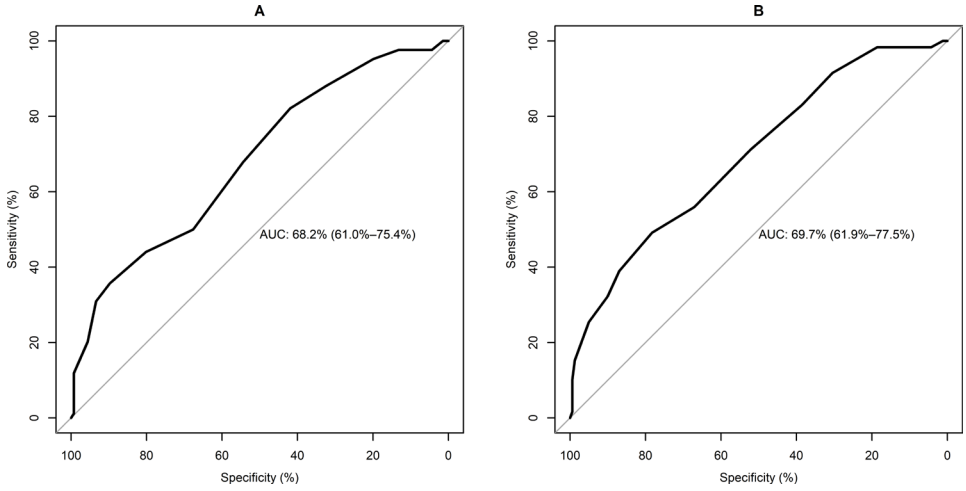

Figure 3 Receiver operating characteristic (ROC) curves for presumption of gestational diabetes mellitus (GDM) prediction (A) and of initiation of pharmacotherapy in GDM (B) by HbA1c levels at early gestation. AUC, area under the curve; HbA1c, hemoglobin A1c.

Table 2 Performance measures of HbA1c ≥5.7%

	GDM	IGDM
Apparent prevalence	0.10 (0.07 to 0.15)	0.10 (0.07 to 0.15)
True prevalence	0.38 (0.32 to 0.45)	0.27 (0.21 to 0.33)
Sensitivity	0.20 (0.12 to 0.30)	0.25 (0.15 to 0.38)
Specificity	0.96 (0.91 to 0.98)	0.95 (0.90 to 0.98)
Positive predictive value	0.74 (0.52 to 0.90)	0.65 (0.43 to 0.84)
Negative predictive value	0.66 (0.59 to 0.73)	0.78 (0.71 to 0.83)

Data are statistical performance measures and 95% CIs.
GDM, gestational diabetes mellitus; HbA1c, hemoglobin A1c; IGDM, insulin-treated gestational diabetes mellitus.

opportunity to identify those women who could benefit of tighter glycemic control at very early stage of gestation. In our study, we could demonstrate that HbA1c >5.7% is associated with lower levels of disposition index, which reflects compensatory effectiveness of beta-cell function in answer to insulin resistance. We further observed that HbA1c is related to later insulin requirement, which is another corroborating aspect for the predictive value of early measured HbA1c.

Since HbA1c is already broadly applied during first routine antenatal visit for detection of pregestational diabetes, implementation of HbA1c in GDM risk stratification becomes an attractive option. Several studies already reported that women with elevated HbA1c during early pregnancy have a higher risk for GDM and/or adverse pregnancy outcomes. In a retrospective analysis Osmundson *et al* showed that risk for GDM was increased by 50% (adjusted RR, 1.48; 95% CI 1.15 to 1.89) in women with first trimester HbA1c of 5.7%–6.4% compared with women with an HbA1c in normal range.[17] Other studies concluded similarly that HbA1c levels referred for pre-diabetes outside of pregnancy are associated with GDM manifestation and hereby supported the prognostic applicability of HbA1c in GDM risk prediction.[6 7 18] Of interest, in a very recent retrospective cohort study pregravid HbA1c measured at median 1.4 years before pregnancy was shown to be a robust predictor of GDM. For each 0.1% elevation of pregravid HbA1c the odds of GDM in a subsequent pregnancy was increased by 22%—however, the authors could not define a threshold for pregravid HbA1c that is implementable to reduce the burden of OGTT screening during pregnancy.[19]

Similar to our findings, several previous studies concluded an overall limited predictive ability of HbA1c at prediabetic level.[6 7 17–19] After reviewing indicated test characteristics of former studies we could detect limitations in comparability of these to our results mainly due to the differences in study design. Our observations of a relatively high specificity but low sensitivity at an HbA1c cut-off of 5.7% for GDM development are very similar to the findings of the retrospective study by Osmundson *et al*, who equally used the IADPSG criteria for GDM diagnosis and applied the same threshold for their analysis.[17] As far as applicable, we could further extract similar test characteristics (ie, specificity and sensitivity) for a cut-point of 5.7% from studies, which differ regarding to diagnosis criteria (ie, the two-step screening by Carpenter and Coustan criteria with preceding challenge test) and the primary choice of a lower threshold.[7 20 21] Further, it has to be considered that HbA1c changes throughout pregnancy[7] which may explain why only moderate correlations are detectable between early HbA1c and glucose examinations in third trimester. However, we are now confronted with the challenge that during an outbreak of pandemic disease measures for containment of virulent infection are required, which limit indications for time-consuming OGTTs—here simple algorithms comprising rapidly obtainable parameters would facilitate preparation of temporary guidelines that adequately balance their benefits versus burden in disease management during special conditions. Thus, the actual COVID-19 pandemic shows that it is worth to direct attention towards large-scale studies comparing different approaches for use in exceptional situations.

Moreover, we observed that elevated maternal HbA1c at early pregnancy is associated with a higher risk for delivering LGA infants even after adjustment for GDM status. Hughes *et al* as well found a higher rate of LGA newborns based on population-adjusted percentiles[6] whereas others reported no significant difference in birth weight.[17 21] However, available data are not powered to identify neonatal differences. The use of HbA1c during early pregnancy represents average glucose level over the prior 3 months and thus might be a better predictor of very early influences on fetal development that are not covered by mid-pregnancy to late pregnancy glucose-based testing. Of further interest is if any early intervention based on maternal HbA1c brings a benefit for pregnancy and/or neonatal outcome—but this aspect is so far not sufficiently addressed in randomized trials. In a study with small sample size it was shown that early treatment for women with HbA1c in prediabetic range did not significantly reduce overall rate of GDM diagnosis in 24th–28th GWs but in a subgroup analysis of non-obese women, GDM risk was decreased by 50%.[22] Recently, Roeder *et al* aimed to examine the effects of early treatment on neonatal hyperinsulinemia and fat mass in women with HbA1c ≥5.7% and/or fasting glucose ≤92 mg/dL. The study stopped early because of low enrollment but presented data showed so far no significant benefit.[23] In another study, investigators randomized obese women to compare early screening prior to 20th week to routine screening, whereby women with HbA1c between 6.2% and 6.5% at initial contact were provided with early screening regardless of randomization arm. Altogether, they found no reduction of composite perinatal outcome between in those who received early screening.[24]

Current recommendations mostly fail to consider women with pre-existing deteriorations in glucose hemostasis who enter pregnancy with glucose elevations below the threshold used for overt diabetes. Further, lack of agreement on uniform screening standards during early pregnancy additionally hardens comparability of studies aiming to characterize high-risk pregnancies. In summary, our data show that early HbA1c ≥5.7% but below overt diabetes reflects

impairments in beta-cell function and glucose disposal that are indicative for underlying defects in compensation mechanisms and risk for early GDM. These associations on pathophysiological level argue for the utility of HbA1c as early predictor for pregnancies at glucometabolic risk that warrant further research.

Contributors LB and AKW conceived the study. Data assessment and patient recruitment were performed by LB, KL and CSG. Statistical analysis, calculations and data interpretation were performed by CSG and LB. The manuscript was written by LB. CSG, GP and AKW reviewed and edited the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This study was approved by the Ethics Committee of the Medical University of Vienna on 19 February 2009 (reference number: 771/2008) and performed in accordance with the Declaration of Helsinki. All participants gave written informed consent to participate in this study.

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