

CORRESPONDENCE

Research Letter

HbA_{1c} Measurement Cannot Replace an Oral Glucose Tolerance Test for the Diagnosis of Gestational Diabetes

In 2020 the coronavirus pandemic had a sustained effect on everyone’s lives. Protecting vulnerable patient groups against Covid-19 presents a challenge in routine clinical practice. Pregnant women are a particularly vulnerable group (1). Between the 24th and 28th weeks of gestation they are tested for gestational diabetes (GDM) and if required they receive a diagnostic oral glucose tolerance test (OGTT) with 75 g glucose (2). To streamline this approach during the pandemic, Meek et al deployed an alternative testing strategy to the oral glucose tolerance test (3). In three British cohorts they investigated whether measuring fasting glucose levels or determining HbA_{1c} at the end of the second/beginning of the third trimester is suitable for identifying women at risk of an unfavorable pregnancy outcome. The authors suggest for the 28th week an HbA_{1c} cut-off of 39 mmol/moL (5.72%) to detect GDM. We investigated the generalizability of this approach to the healthcare services for pregnant women in Germany.

Methods

We tested the suggested strategy in participants of the ongoing German Gestational Diabetes Study (PREG-Study, Clinical Trials.gov Identifier NCT04270578). In this study, pregnant women between the 24th+0 and 31st+6 weeks of gestation received a 2 h OGTT with 75 g glucose. Venous plasma glucose concentrations were measured at fasting, as well as 1 and 2 hours after glucose ingestion, in a quality controlled manner. HbA_{1c} was measured by HPLC. GDM was diagnosed following IADPSG consensus recommendations (4), which were included in the German guideline GDM (2). If at least one of the three blood glucose measurements was above the cut-off value, a diagnosis of GDM was made (Table 1). In addition to anthropometric data during the pregnancy, data on the pregnancy outcome were collected. In case of a diagnosis of GDM, the women were treated according to the guideline until delivery (2). The PREG Study was approved by Tübingen University’s ethics committee.

Results

A total of 118 cases of GDM were diagnosed among 440 pregnancies. When the HbA_{1c} cut-off of 39 mmol/moL (5.72%) suggested by Meek et al was applied, GDM was discovered in 12 women (Table 2). In 106 women, GDM was not diagnosed according to this criterion. Eight women with a normal glucose metabolism had an HbA_{1c} measurement above this cut-off. The specificity of the suggested HbA_{1c} cut-off value is 97.5%, but its sensitivity is only 51.2%. Using a lower cut-off of 32 mmol/moL could increase the sensitivity to 78%, but the specificity would then be only 51.2%. When applying the slightly different criteria from Britain’s National Institute for Health and Care Excellence (NICE), 104 women had a diagnosis of GDM (rare than 118). Of these, only eight had an HbA_{1c} measurement above 39 mmol/moL. Compared with women with GDM and low HbA_{1c}, those

TABLE 1

Blood glucose cut-off values for diagnosing gestational diabetes mellitus by using 75 g oral glucose tolerance test (2)

Timing	Cut-offs venous plasma (mg/dL)	Cut-offs venous plasma (mmol/L)
Fasting	92	5.1
After 1 h	180	10
After 2 h	153	8.5

with HbA_{1c} >39 mmol/moL had a fasting glucose concentration that was 0.5 mmol/L (± 0.04) higher, whereas the values after glucose intake were comparable. The two groups also differed in terms of the anthropometric parameters of the mothers (Table 2).

Among the pregnant women with low HbA_{1c}, those with GDM did not only have higher blood glucose concentrations before and during the OGTT, but they were also older and heavier. Although the HbA_{1c} of these women with GDM was still below the cut-off suggested by Meek et al, HbA_{1c} was higher than in women with a normal glucose metabolism (Table 2).

Furthermore, appropriate treatment after the diagnosis of GDM resulted in normal birth weight.

Discussion

Our analysis shows that in the second and third trimester, an HbA_{1c} value above 38 mmol/moL (5.72%) is not suitable for making a diagnosis of GDM. Most patients with GDM (89.8%) would have been overlooked if this approach had been used and would not have been treated. Even when a lower HbA_{1c} cut-off (32 mmol/moL) had been applied, about one fifth of GDM cases would have remained undetected.

Using an HbA_{1c} cut-off identifies primarily women with a high fasting glucose concentration, whereas women with high postprandial glucose levels but normal fasting glucose are often missed. But it is precisely these high glucose peaks that cause excess insulin secretion in the fetus, which promotes fetal overgrowth. The current recommendations for screening for GDM are based mainly on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study (5). By examining more than 23 000 participants this study showed that even moderately raised blood glucose levels were associated with a clearly increased risk for macrosomy, neonatal hypoglycemia, and cesarean section. Consistent treatment of women with only moderately raised HbA_{1c} can likely reduce rates of this complications.

TABLE 2

Characteristics of pregnant women and neonates*

Parameter	Normal glucose tolerance (n = 322)	GDM (HbA _{1c} < 39 mmol/mol) (n = 106)	GDM (HbA _{1c} ≥ 39 mmol/mol) (n = 12)
OGTT			
Glucose min 0 (mmol/L)	4.33 [4.11; 4.56]	4.72 [4.50; 5.17]	5.36 [5.03; 5.86]
Glucose min 60 (mmol/L)	7.56 [6.47; 8.50]	10.53 [9.58; 11.30]	10.53 [9.49; 11.46]
Glucose min 120 (mmol/L)	6.06 [5.28; 6.83]	8.50 [7.42; 9.33]	7.86 [7.33; 8.33]
HbA _{1c} (mmol/mol)	31.00 [29.00; 34.00]	34.00 [32.00; 35.00]	40.00 [39.75; 42.00]
HbA _{1c} (%)	5.00 [4.80; 5.20]	5.25 [5.00; 5.40]	5.80 [5.77; 6.00]
Maternal parameters			
Age (years)	32 (5)	33 (5)	34 (7)
Parity (%)			
Nulliparous	182 (56.5)	47 (44.3)	4 (33.3)
Multiparous	140 (43.5)	59 (55.7)	8 (66.7)
BMI before conception (kg/m ²)	24.4 (5.0)	27.4 (5.9)	33.9 (6.4)
BMI at the time of the OGTT (kg/m ²)	27.2 (4.7)	29.9 (5.6)	35.6 (7.0)
Body fat at the time of the OGTT (%)	39.2 (8.7)	41.2 (8.7)	48.8 (4.0)
Gestational age at the time of the OGTT (in weeks)	27.51 (2.47)	27.64 (2.34)	27.25 (1.82)
Weight gain during pregnancy up to OGTT (kg)	7.4 (4.2)	7.0 (4.1)	5.5 (5.2)
Neonatal parameters			
Length at birth (cm)	51.3 (2.6)	50.4 (3.0)	50.3 (1.5)
Weight at birth (g)	3 421 (508)	3 241 (490)	3 393 (503)

*Data are shown as means (standard deviations), as medians [interquartile range] or integers (%). BMI, body mass index; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test.

Conclusions

Even if an alternative, low-contact testing strategy is desirable during the pandemic, this should not happen at the expense of the mothers's and child's long-term health. Measuring HbA_{1c} alone in the second and third trimester cannot be a substitute for oral

glucose tolerance testing to diagnose GDM. A diagnostic OGTT remains the most reliable approach for identifying affected patients and timely initiate optimal treatment.

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Conflict of interest statement

A Fritsche received consulting fees from von Sanofi, Novo Nordisk, Astra Zeneca, and Boehringer Ingelheim.

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L Fritsche, A Peter, J Hummel, H-U Häring, A L Birkenfeld, and R Wagner declare that no conflict of interest exists.

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