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Glycated albumin in pregnancy correlates negatively with body mass index and contributes to the risk of gestational diabetes mellitus

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ABSTRACT

Objectives: The aims of our study were to establish a reference interval for glycated albumin (GA) in gestational week 30, to investigate whether GA can replace or reduce the need for oral glucose tolerance test (OGTT) in pregnancy, and to reassess the usefulness of body mass-index (BMI), age and fasting glucose in detection of gestational diabetes (GDM).
Design: and methods: We measured GA in 486 healthy pregnant women. Reference interval was calculated using the central 95 % of the results. ROC curves were created to assess the ability of GA, fasting glucose and BMI separately to detect GDM, and logistic regression analysis was used to estimate risk of developing GDM given the level of the same markers. Finally, multiple logistic regression analysis based on GA, fasting glucose and BMI was used to find a strategy of predicting a patient's risk of GDM.
Results: The reference interval for GA at week 30 of gestation is 6.8–10.3 %. The analysis has a low AUC (0.53) with respect to detecting GDM. It increases slightly to 0.64 when corrected for BMI, as GA is inversely correlated to BMI. Combining GA with fasting glucose and BMI at gestational weeks 16–20 could raise the AUC to 0.80.
Conclusion: GA cannot be recommended to replace OGTT for the diagnosis of GDM. Nor can it be used to identify women at risk of developing GDM. GA combined with fasting glucose and BMI in early pregnancy could be a useful model to estimate risk of GDM.

1. Introduction

Glycated hemoglobin A1c (HbA1c) is the primary analysis for diagnosis and follow-up of diabetes mellitus, reflecting the average

Abbreviations: HbA1c, Glycated hemoglobin A1c; GA, glycated albumin; OGTT, oral glucose tolerance test; GDM, gestational diabetes mellitus; SUS, Stavanger University Hospital; LC-MS/MS, liquid chromatography-tandem mass spectrometry; NFFD, Norwegian Fit For Delivery study; BMI, body mass index; CLSI, Clinical and Laboratory Standards Institute; ROC, receiving operating characteristic; GFR, glomerular filtration rate.

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level of plasma glucose over the previous 8–12 weeks. For some patient groups, however, the HbA1c may be misleading, most often artificially low [1]. The biggest source of error in this context is altered erythrocyte lifespan. Certain hemoglobin variants will also interfere with the HbA1c methods and lead to false results [2]. Pregnancy is one of the conditions where HbA1c is not very suitable for assessing long term glucose levels [1], because of increased erythropoietin production, an increased proportion of young erythrocytes and relative iron deficiency. Changes in blood glucose levels occur relatively fast in pregnant women, and HbA1c thus fails to capture these changes.

For some of the patient groups where HbA1c has a limited value (hemolytic disease, renal failure), glycated albumin (GA) has shown to be useful [3,4]. Albumin is glycated by a spontaneous reaction where glucose links to an amino group [5], and the degree of glycation depends on the degree of glycaemia. The value of GA represents the level of glycaemia over the last 2–3 weeks, it should therefore be better suited to follow patients with altered erythrocyte lifespan, and in cases where there are faster changes in blood glucose levels. One might therefore assume that the analysis can be useful in pregnancy.

According to the current guidelines (2017) for prenatal care in Norway, the oral glucose tolerance test (OGTT) is offered to pregnant women in gestational week 24–28, if they are defined as being at increased risk of developing gestational diabetes mellitus (GDM) [6]. Risk factors currently include age >25 years for first-time mothers, body mass index (BMI) > 25, family history of diabetes, and ethnic background from Asia and Africa. A lower age and BMI cut-off compared to earlier guidelines has led to a significant increase in the proportion of women offered OGTTs, from approximately 25 % (2009 guidelines) to an estimated 70 % of all pregnancies (current guidelines) [6], which is both time- and resource-consuming. It is therefore relevant to investigate whether GA can improve the detection of women at risk for GDM and thereby reduce the need for OGTTs.

Currently, only Stavanger University Hospital (SUS) performs GA-analysis in Norway, measured with liquid chromatography-tandem mass spectrometry (LC-MS/MS) [7]. They recently established a reference interval for healthy first-time pregnant women (N = 121) in gestational weeks 24–28 [8]. The result showed that the reference interval for pregnant women was slightly lower than for non-pregnant women. They also found that GA was poorly suited to diagnose GDM. However, the population at SUS consisted exclusively of women referred to an OGTT because they were at risk of developing GDM according to Norwegian guidelines. Hence, healthy pregnant women ≤25 years with ethnic background for Europe and BMI <25 were not included in the study.

Reference interval of GA in pregnant Italian women was also recently published [9]. Similar to SUS's study [8] and Asian studies [10], the GA reference interval in the Italian study were lower in pregnant women than in non-pregnant women. There are several Asian studies on GA in pregnant women with pre-existing diabetes, showing that GA is a useful marker for glycemic control and for predicting pregnancy outcome [11,12]. However, some studies have been inconclusive with regard to benefit in GDM [10,13]. A recent American study found that GA was not a sensitive test to detect hyperglycemia in pregnancy [14]. There is thus a need to expand the knowledge about GA during pregnancy, and to further explore its usefulness in GDM.

Our aim was to establish a reference interval for GA in week 30 of pregnancy in a larger Norwegian cohort, and compare this with previous findings. We also aimed to investigate whether there is a statistical difference in the level of GA in individuals with and without GDM, and between individuals with and without risk factors of GDM. Finally, we assessed the potential of GA to replace or reduce the need for OGTT in pregnancy. For this purpose, we analyzed whether GA, either alone or in combination with known risk factors (age, BMI) or fasting glucose, can detect or predict GDM as defined by Norwegian guidelines from 2017.

2. Material and methods

2.1. Study population

The Norwegian Fit For Delivery study (NFFD) is a randomized controlled trial performed in Southern Norway that examined the effect of a lifestyle intervention on pregnancy outcomes, including gestational weight gain and newborn birth weight [15,16]. 606 healthy women expecting their first child were included between 2009 and 2013, and age, self-reported pre-pregnancy weight, measured height at inclusion and calculated body mass index (BMI) were recorded.

Since all the participants were healthy pregnant women, and the intervention involved only lifestyle advice/measures, we considered it appropriate to include both the intervention and control groups in the establishment of the reference interval. Although we have seen that GA is negatively correlated with BMI, we chose to include everyone regardless of BMI because all participants were perceived as healthy pregnant women upon inclusion.

2.2. Sample processing and measurement

Blood samples were taken at study inclusion (gestational weeks 16–20) and at gestational week 30 in NFFD. All glucose measurements were done on Cobas 6000 (Roche) at Sørlandet Hospital. The first sample was drawn on a serum tube (Greiner Bio-one), centrifuged after 30 min before transportation, and fasting glucose was measured.

In week 30, the sample for glucose measurement was drawn on Lithium-Heparin tubes (Greiner Bio-one), then centrifuged immediately before plasma was transferred to a second tube without additives. Fasting glucose and glucose 2 h after consuming 75g of glucose (i.e. OGTT) were measured. In addition, an extra serum sample was drawn, and then frozen at −80 °C for later use.

Serum samples from gestational week 30 were sent frozen to SUS for analysis of GA with LC-MS/MS.

2.3. Gestational diabetes criteria

The diagnosis of GDM was made in the original NFFD study based on the guidelines in use at the time, both nationally and internationally, as recommended by the WHO (1999): an OGTT with fasting glucose ≥7,0 mmol/L and/or 2-h value ≥ 7,8 mmol/L were considered diagnostic of GDM [17]. However, for the current study, we used the updated national guidelines (2017) for defining GDM: an OGTT with fasting glucose ≥5.3 mmol/L and/or 2-h value ≥ 9.0 mmol/L.

2.4. Statistical methods

For the calculation of the GA reference interval, participants who retrospectively met the current national criteria for gestational diabetes were excluded. The distribution of the remaining results was checked for normality and then presented as mean and 2.5 and 97.5 percentiles. Ninety percent confidence intervals for the reference limits were also calculated. The conventional reference interval was thus determined according to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) [18]. Age >25 years and/or pre-pregnancy BMI >25 kg/m2 were used to dichotomize participants into the categories "GDM-risk" or "no GDM-risk". Two-sided t-tests for continuous data and chi-squared tests for proportions were employed to test for differences between independent groups. BMI-adjusted GA percentiles and z-scores were calculated using an LMS method [19]. Logistic regression was performed to estimate the risk of GDM given the results of the continuous parameters age, BMI, fasting glucose in gestational weeks 16–20 and BMI-adjusted GA z-score. Individual ROC curves were constructed for each parameter. Multiple logistic regression models were then used to combine these parameters. ROC curves and classification tables were generated, the latter at a diagnostic sensitivity set to 95 %. A likelihood ratio test was used to compare the fit of multiple regression models. A significance level of 5 % was set for all tests. Results were processed in Excel/Analyse-IT 4.6, GraphPad Prism 10.1.2 and LMS Chartmaker Pro 2.54.

The Norwegian Regional Committee for Medical Research Ethics South-East–C approved the NFFD trial (REK reference 2009/429). All participants have provided informed, signed consent.

3. Results

3.1. Description of participants

Samples from 30th week of gestation were available for 557 of the participants, with nearly complete data sets from 525/557. One participant was excluded from all analyses because she was diagnosed with pre-existing diabetes mellitus, hence data from 524 participants remained. Thirty-eight participants were retrospectively diagnosed with GDM. Therefore, samples from 486 participants were used for establishing a reference interval for GA. Nine of the participants did not have fasting glucose at inclusion.

Participants retrospectively diagnosed with GDM (N = 38) were on average slightly older, had a higher BMI and higher serum glucose levels at gestational week 16–20 than non-GDM individuals (Table 1.) The proportion of patients with GDM was not statistically significantly different between the GDM-risk and no-risk groups. Six of the 38 women retrospectively diagnosed with GDM were not at risk for GDM with respect to age and BMI, and would have been missed by the current guidelines.

3.2. Glycated albumin

3.2.1. Distribution and conventional reference interval

Fig. 1 presents the overall distribution of results for GA in pregnancy week 30. The distribution is approximately normally distributed, and the conventional reference interval for GA in pregnancy week 30 is 6.8–10.3 %.

Table 1
Description of participants. Gestational diabetes is diagnosed by 2017 Norwegian guidelines, i.e. an OGTT with fasting glucose ≥5,3 mmol/L and/or 2-h value ≥ 9.0 mmol/L. GDM risk: Age >25 years and/or BMI >25; *between GDM and Not GDM; **: The difference between these proportions is not statistically significant, p = 0.33; n.a.: not applicable.

	Total, n = 524	GDM, n = 38	Not GDM, n = 486	p-value*
Age at inclusion (years), mean (SD)	28.0 (4.3)	29.7 (5.3)	27.9 (4.2)	<0.05
Pre-pregnant BMI, mean (SD)	23.6 (3.8)	26.6 (5.1)	23.4 (3.6)	<0.01
Fasting glucose week 16–20 (mmol/L), mean (SD)	4.4 (0.4)	4.8 (0.4)	4.4 (0.4)	<0.01
Fasting glucose week 30 (mmol/L), mean (SD)	4.6 (0.4)	5.4 (0.4)	4.6 (0.3)	<0.01
2-h glucose week 30 (mmol/L), mean (SD)	6.1 (1.2)	7.9 (1.6)	5.9 (1.1)	<0.01
	n	*n*	*n*	*GDM %*
GDM risk	408	32	376	7.8**
No GDM risk	116	6	110	5.2**
GDM diagnosed via fasting glucose week30	29	29	n.a.	n.a.
GDM diagnosed via 2-h glucose week 30	9	9	n.a.	n.a.

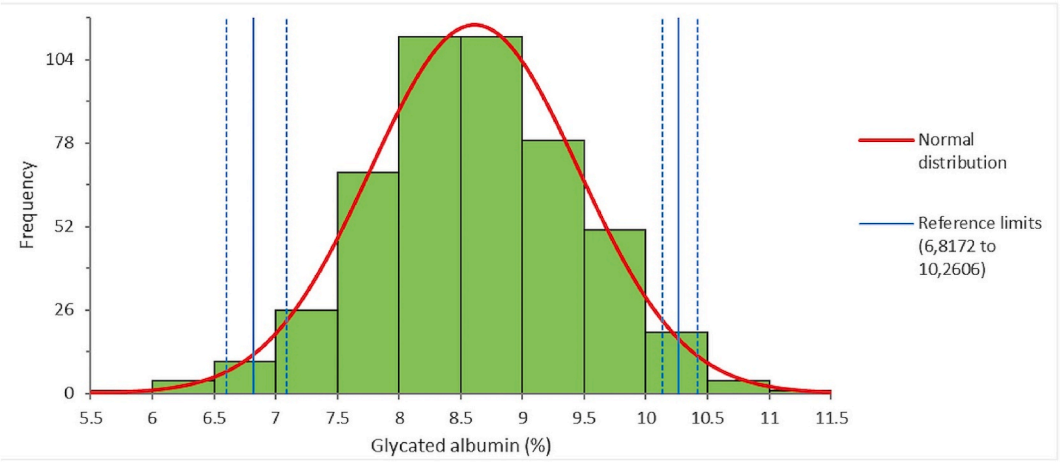


Fig. 1. Distribution of glycated albumin, N = 486. Vertical lines indicate 2,5 and 97,5 % percentiles, and dashed lines indicate their 90 % confidence intervals. Mean value 8,6 %, the 2.5. and 97.5 percentiles correspond to 6.8 % and 10.3 %, respectively.

3.2.2. Glycated albumin by risk and diagnosis

The mean level of GA in participants with and without GDM, and with and without risk factors of GDM is summarized in Table 2. We found no statistically significant difference in GA between the groups. We found no correlation between age and GA, and, accordingly, no difference in GA at ages below and above 25 years (data not shown). Glycated albumin was negatively correlated to BMI (Fig. 2). Consequently, there was also a difference between the groups with BMI below and above 25 kg/m^2. Average GA in the normal weight group (N = 380) was 8.8 % (90 % CI: 8.7–8.8), while average GA in overweight/obese group (N = 144) was 8.2 % (90 % CI: 8.1–8.3), $p < 0.01$.

Table 3 shows glycated albumin z-scores adjusted for body-mass index. For patients with a retrospective diagnosis of GDM, the mean z-score was +0.46, whereas for those without GDM it was −0.04, a highly significant difference ($p < 0,01$). In the following, GA standardized for BMI as z-scores will be addressed to as "BMI-adjusted GA".

3.2.3. BMI-adjusted glycated albumin as a risk factor for gestational diabetes

The estimated risk of developing gestational diabetes based on BMI-adjusted GA, fasting s-glucose at gestational weeks 16–20, BMI and age, respectively, are shown in Fig. 3. It appeared that BMI-adjusted GA, like age, was only weakly associated with GDM risk and the association was largely uncertain. BMI and fasting glucose appeared to be moderately associated with GDM risk. The risk of developing GDM was low for BMI <24 and fasting glucose <4.5 mmol/L. The risk, but also the uncertainty, increased with increasing values.

3.2.4. BMI-adjusted glycated albumin as a diagnostic test for gestational diabetes

Regarding the ability to detect GDM, Fig. 4 presents BMI-adjusted GA, BMI, age and fasting glucose at gestational weeks 16–20 against diagnosed GDM in different ROC curves. In our study population neither age nor unadjusted GA (data not shown) were able to detect GDM. The AUC for unadjusted GA was 0.53 (0.44–0.63). Neither were statistically significantly different from 0.50. The discriminatory power of BMI-adjusted GA and BMI seemed to be poor, for fasting glucose moderate [20].

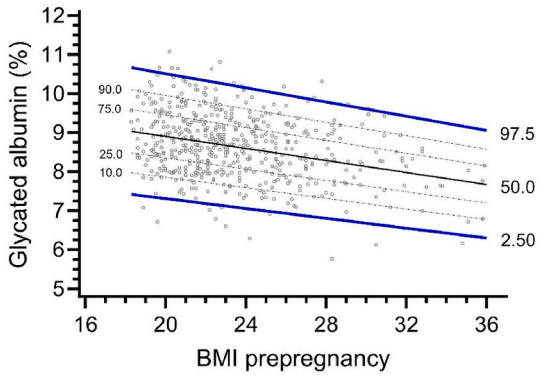
3.3. Multiple logistic regression models for prediction of gestational diabetes

ROC-curves of multiple logistic regression models and classification tables of the combined parameters BMI and glucose at gestational weeks 16–20, alone and with the addition of GA are presented in Fig. 5 and Table 4. We did not include age in these calculations as it appeared to contribute least to the prediction of GDM.

Combining pre-pregnancy BMI and fasting glucose at gestational weeks 16–20 allowed for a diagnostic specificity of 35 % at a diagnostic sensitivity of 95 %, a negative predictive value (NPV) of 99 % and a positive predictive value (PPV) of 10 %. Adding GA to

Table 2
Glycated albumin by risk and diagnosis. GDM: gestational diabetes. GA: glycated albumin. SD: standard deviation. GDM risk: age>25 and/or BMI>25. There are no statistically significant differences between groups.

	Total, n = 524	GDM, n = 38	Not GDM, n = 486
GA (%) overall, mean (SD)	8.6 (0.8)	8.7 (0.8)	8.6 (0.8)
GA (%) GDM risk, mean (SD)	8.6 (0.9)	8.7 (0.8)	8.6 (0.9)
GA (%), no GDM risk, mean (SD)	8.7 (0.8)	9.0 (0.9)	8.6 (0.8)



BMI	GA Percentiles		
	2.5%	*50.0%*	*97.5%*
18	7.4	9.0	10.7
20	7.3	8.9	10.5
22	7.2	8.7	10.3
24	7.1	8.6	10.1
26	6.9	8.4	10.0
28	6.8	8.3	9.8
30	6.7	8.1	9.6
32	6.6	8.0	9.4
34	6.4	7.8	9.2
36	6.3	7.7	9.1

Fig. 2. Percentiles for glycated albumin related to body mass index. BMI: body mass index, GA: glycated albumin.

Table 3
Glycated albumin z-scores adjusted for body mass index, by risk and diagnosis. GA: glycated albumin. GDM: gestational diabetes. SEM: standard error of mean. GA z-score: Glycated albumin z-scores standardized for BMI; GDM risk: age>25 and/or BMI>25. *p < 0.01 between GDM and not GDM.

	Total, n = 524	GDM, n = 38	Not GDM, n = 486	p-value*
GA z-score overall, mean (SEM)	0.00 (0.04)	+0.46 (0.16)	−0.04 (0.05)	<0.01
GA z-score GDM risk, mean (SEM)	+0.03 (0.05)	+0.47 (0.17)	0.00 (0.05)	<0.01
GA z-score, no GDM risk, mean (SEM)	−0.13 (0.09)	+0.43 (0.45)	−0.16 (0.09)	0.16

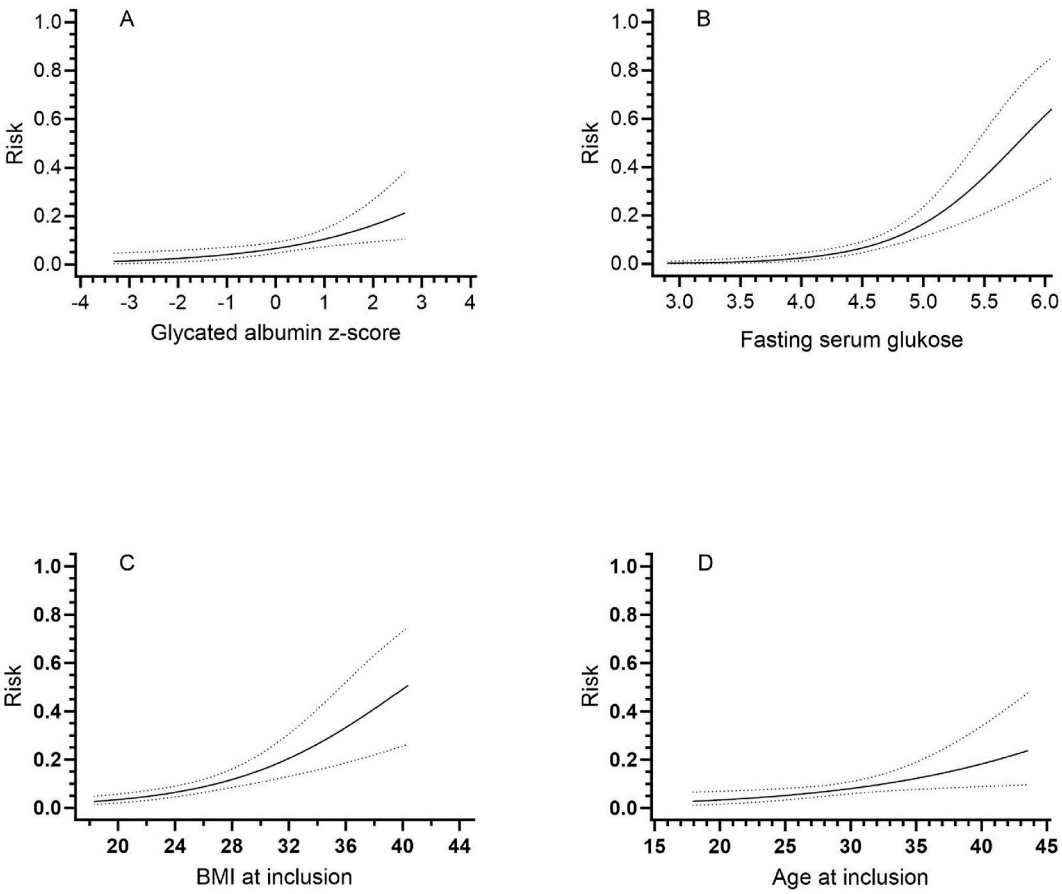


Fig. 3. Estimated risk of developing gestational diabetes based on A: BMI-adjusted glycated albumin, B: fasting glucose at gestational weeks 16–20, C: body mass index, D: age. The dashed lines indicate the 95 % confidence interval.

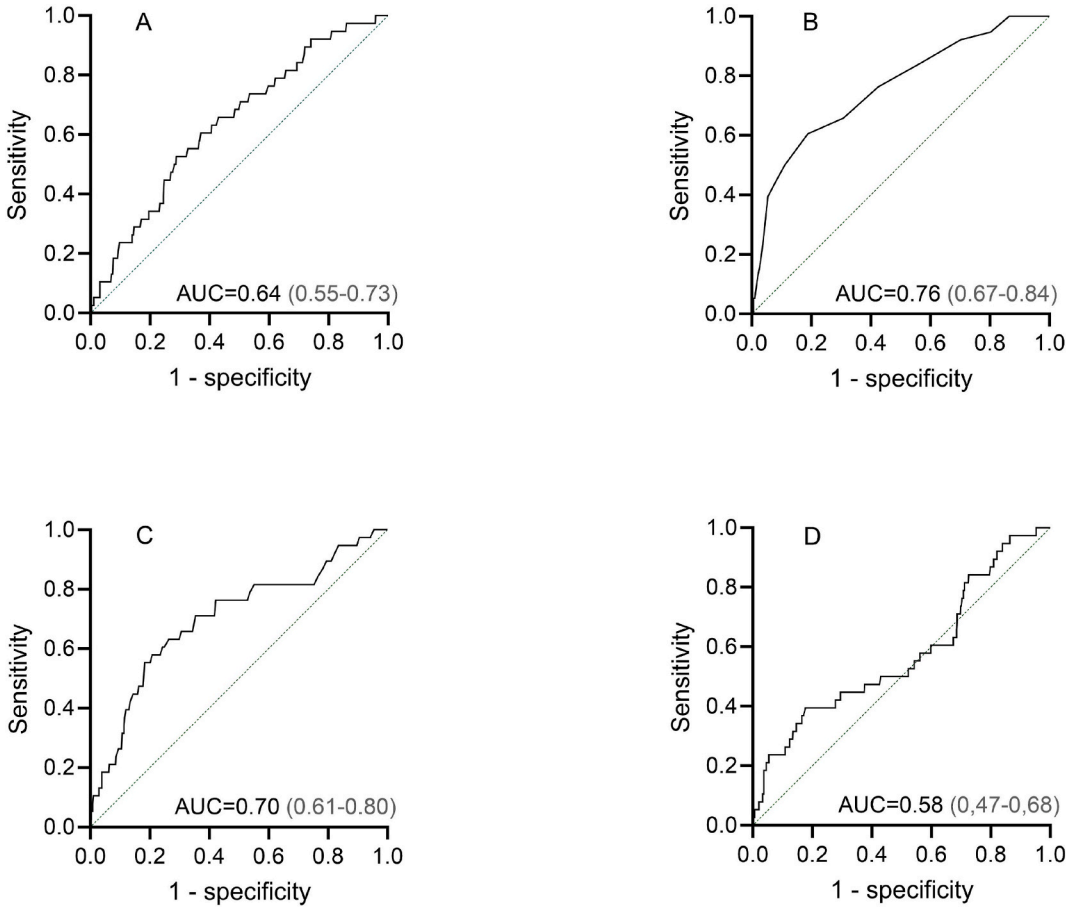


Fig. 4. Diagnostic performance for detection of gestational diabetes shown by ROC-curves of A: BMI-adjusted glycated albumin, B: fasting glucose at gestational weeks 16–20, C: body mass index and D: age. BMI: body mass index, AUC: area under the curve.

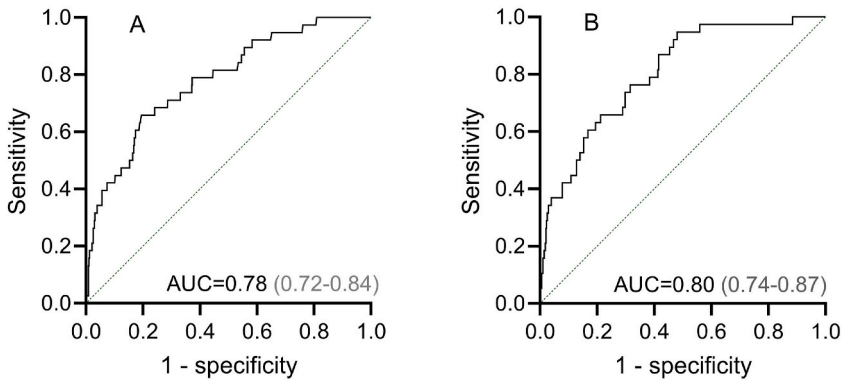


Fig. 5. ROC-curve of multiple logistic regression. A: fasting glucose and BMI at gestational weeks 16–20. B: Fasting glucose and BMI at gestational weeks 16–20; glycated albumin week 30. BMI: body mass index. AUC: area under the curve.

the model slightly increased the AUC from 0.78 to 0.80, specificity to 52 % and PPV to 14 % at the same diagnostic sensitivity. The difference between these two models was statistically significant (likelihood-ratio 8.5, $p < 0.01$). For comparison, fasting glucose alone had a diagnostic sensitivity of 76 %, a specificity of 57 %, a NPV of 97 % and a PPV of 13 % at a cut-off of 4.5 mmol/L (data not shown).

Table 4
Classification tables of combined parameters' ability to predict gestational diabetes at a diagnostic sensitivity set to 95 %. A: fasting glucose and BMI at gestational weeks 16–20. B: Fasting glucose and BMI at gestational weeks 16–20, glycated albumin week 30. BMI: body mass index.

A	Fasting glucose week 16–20 and BMI for prediction of gestational diabetes		
	Predicted no	Predicted yes	Total
Observed no	166	311	477
Observed yes	2	36	38
Total	168	347	515
Diagnostic sensitivity (%): 95			
Diagnostic specificity (%): 39			
Negative predictive value (%): 99			
Positive predictive value (%): 10			

B	Glycated albumin, fasting glucose week 16–20 and BMI for prediction of gestational diabetes		
	Predicted no	Predicted yes	Total
Observed no	247	230	477
Observed yes	2	36	38
Total	249	266	515
Diagnostic sensitivity (%): 95			
Diagnostic specificity (%): 55			
Negative predictive value (%): 99			
Positive predictive value (%): 14			

4. Discussion

We found a higher GA in the normal weight group compared to the overweight/obese group, otherwise there were no differences in GA level between the different groups. GA showed no ability alone to diagnose GDM, but there could be a potential of using GA together with BMI and glucose in estimating risk of developing GDM.

The GA reference interval for pregnant women at week 30 of gestation was lower than for non-pregnant women and slightly lower than that found at SUS in pregnant women weeks 24–28. This is in line with Asian studies [10,21] and an Italian study [9], and thus matched our expectations. Several mechanisms can potentially cause the relatively low GA during pregnancy. In addition to lower levels of circulating glucose, one cause might be increased turnover of albumin and an increased glomerular filtration rate. Paleari et al. [22] found that the proportion of GA decreased more than total albumin throughout pregnancy (N = 10), and therefore believe they can support that the drop in GA is not due to the physiological hemodilution that occurs in pregnancy. In contrast, a recently published American study observed that the level of GA remained relatively constant throughout pregnancy [23]. A drop in GA concentration occurred only in late pregnancy (week 33–39 of gestation), and this was consistent for all ethnicities investigated. More knowledge is thus needed about normal values of GA throughout pregnancy. The study from SUS showed a tendency for GA to decrease over the course of pregnancy for patients with GDM (n = 18), but so far it has not been examined for healthy pregnant women in the Nordics.

The difference we found from weeks 24–28 (SUS) and week 30 (NFFD) could theoretically represent differences in the populations. As mentioned, the population in NFFD contained healthy pregnant women of all ages, while the population at SUS exclusively contained pregnant women who were at risk of developing GDM. The SUS population was thus very similar to our GDM risk group. Since the GA level was virtually identical between the GDM risk and no risk groups in NFFD, whilst the mean GA was 9,5 % in SUS study against 8,6 % in NFFD, there is reason to believe that gestational length is the most important cause of the difference between GA level in the studies.

We found no correlation between age and GA. However, the connection between GA and BMI was clear, as has also been seen in previous studies for people both with and without diabetes [24,25]. The cause for this is unknown, but a possible explanation could be a faster turnover of albumin in overweight and obese people, partly because of a low-grade inflammation in these conditions. Another recent study presented an alternative explanation: obesity-related changes in the molecular environment surrounding albumin [26]. This inverse association helps explain why the analysis is unsuitable for detecting gestational diabetes, especially in overweight/obese patients.

In our study, we defined GDM according to the current national guideline from 2017. The diagnostic criteria are based on the HAPO-study (Hyperglycemia and Adverse Outcomes in Pregnancy) from 2008 [27], as are the diagnostic criteria in both WHO 2013 guidelines [28] and International Association of Diabetes and Pregnancy Study Group (IADPSG) guidelines from 2010 [29]. However, the glucose cut-off values of the Norwegian guidelines differ somewhat from cut-off values in WHO and IADPSG guidelines. In Norway, fasting and 2-h glucose values are measured and the glucose cut-offs were set to include women with a 100 % greater risk of having adverse pregnancy outcome compared to the average (OGTT with fasting glucose $\geq$5.3 mmol/L and/or 2-h value $\geq$ 9.0 mmol/L defined as GDM), in contrast to IADPSG guideline, which includes three measurements and set the cut-offs to catch those with a 75 % greater risk (OGTT with fasting glucose $\geq$5.1 mmol/L and/or 1-h glucose $\geq$10.0 mmol/L and/or 2-h glucose $\geq$8.5 mmol/L defined as GDM). Hence, fewer women are diagnosed with GDM using Norwegian guideline compared to these international guidelines.

Regarding the ability of GA to detect GDM, we chose to use samples from week 30 for our study because these were drawn at the same time as OGTT was performed and thus probably would be best suited for assessing the potential of GA to replace OGTT. We found the assay to be unsuitable for this purpose, with an AUC of 0.53. Even when adjusting for BMI, the ability of GA to detect GDM is poor (AUC = 0.64). In other words, the analysis is unsuitable for diagnostic purposes and cannot replace OGTT. However, it is not unlikely that GA could replace or supplement HbA1c in the follow-up of pregnant women with pre-existing diabetes. In fact, a recent study that compared GA levels to continuous glucose monitoring in pregnant women with pre-existing diabetes, found that GA was associated with time spent in target range, and that GA was more accurate than HbA1c to detect time above range [30]. There is, however, a long

way to go before the analysis can become a useful tool in prenatal care. More use of GA in clinical practice requires a well-defined goal of treatment for diabetes in the form of a cut-off value for GA, which does not yet exist - neither for non-pregnant women nor for pregnant women. Furthermore, establishing cut-off values would depend on standardizing the different methods for analyzing GA, as has been done for HbA1c.

When it comes to the diagnostic performance of GA in combination with other parametres, it is worth noticing that in recent years, several studies have looked at the possibility of using fasting glucose to assess who should undergo an OGTT, in order to simplify the diagnosing of GDM. Ryser et al. [31] found that a practice of performing OGTT only in patients with fasting glucose levels in a certain interval (4.4–5.0 mmol/l), would avoid OGTT in 64 % of their patients. A recent Norwegian study that used data from the NFFD amongst other trials, found that a strategy of using fasting glucose with a threshold of 4.7 mmol/L, could have the potential to eliminate the need for OGTT in 70–77 % of pregnancies while missing only 7–7.5 % of GDM cases. These missed cases had a low risk of GDM-associated adverse pregnancy outcomes [32]. In the current study, using fasting s-glucose at a cut-off of 5.3 mmol/l in week 30 had a diagnostic sensitivity of 76 %. This was in fact equal to the sensitivity of fasting s-glucose at a cut-off of 4.5 mmol/L at gestational weeks 16–20 for predicting GDM to occur later. Increasing levels in early pregnancy entailed an increasing risk of developing GDM, while fasting s-glucose <4.5 mmol/l at the first pregnancy visit indicated a low risk of developing gestational diabetes, Fig. 3. It is not possible to diagnose GDM in early pregnancy as it occurs in 2nd or 3rd trimester. Nevertheless, it seems that fasting glucose both in early pregnancy and in later pregnancy, regardless of GA, could have the potential to estimate the risk of GDM, thereby reducing the need of OGTT.

Combining BMI and glucose at gestational weeks 16–20 in a multiple logistic regression model allowed for a high NPV (99 %) at a diagnostic sensitivity of 95 % for predicting GDM. This is as high as achieved by adherence to current guidelines in the NFFD cohort: Two of 38 women diagnosed with GDM had no risk factor with respect to age and/or BMI, and additionally a fasting glucose in week 30 < 5.3 mmol/L. On the other hand, this strategy only marginally reduced the frequency of OGTT, to 67 % (347/515), classification Table 4a. It is thus limited how much such a strategy would simplify today's routines. Adding GA to the model allowed to avoid OGTT in about half of the women (48 %) while maintaining a diagnostic sensitivity of 95 % and a NPV of 99 %, classification Table 4b. To be able to assess the relevance of implementing a strategy with a model containing BMI, fasting glucose and GA, we should have had knowledge about GA in early pregnancy. For the time being, it is uncertain whether it is useful to add more parametres to the risk assessment in early pregnancy than is already done.

Our calculations regarding ability of the different parameters to detect or predict GDM are based on the population in FFD, with no more than 38 individuals defined as having GDM. This relatively low number obviously makes the results somehow uncertain. To achieve more reliable results, this should be investigated and confirmed in larger studies.

5. Conclusion

The reference range for GA at 30 weeks of gestation is 6.8–10.3 %, significantly lower in overweight/obese individuals than in normal weight individuals. The analysis itself is not suitable for diagnosing GDM, nor can it identify individuals at increased risk of developing GDM. GA cannot replace OGTT, and its usefulness in pregnancy is otherwise still uncertain. GA combined with fasting glucose and BMI in early pregnancy could be a useful model to estimate risk of GDM. Fasting glucose in early pregnancy could be given greater weight in assessing whether a woman should undergo OGTT, thereby reducing the number of OGTTs.

CRediT authorship contribution statement

Toril Ø. Osestad: Writing – original draft, Investigation, Conceptualization. **Kristin Lilleholt:** Writing – review & editing, Supervision, Conceptualization. **Øyvind Skadberg:** Supervision, Methodology. **Linda R. Sagedal:** Writing – review & editing, Supervision, Conceptualization. **Ingvild Vistad:** Writing – review & editing, Supervision, Conceptualization. **Thomas Hundhausen:** Writing – review & editing, Investigation, Formal analysis, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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