Association between glycated albumin, fructosamine, and HbA1c with neonatal outcomes in a prospective cohort of women with gestational diabetes mellitus

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Abstract
Objective: To investigate whether glycated albumin, fructosamine, and hemoglobin A1c (HbA1c) are associated with neonatal complications in newborns of pregnant women with gestational diabetes mellitus (GDM).

Methods: Between November 2016 and September 2017, women with a singleton pregnancy and GDM were enrolled in a prospective study in an obstetric Portuguese referral center. Glycemic markers were compared between mothers of newborns with and without complications. Multivariable logistic regression models and corresponding areas under the receiver operating characteristic curve (AUC) were used.

Results: A total of 85 women participated in the study. Raised levels of glycated albumin and fructosamine were associated with at least one neonatal complication (OR- [odds ratio] estimate: 1.33, P=0.015; OR: 1.24, P=0.027, respectively) and with respiratory disorders at birth (OR 1.41, P=0.004; OR 1.26, P=0.014, respectively). HbA1c was not associated with these outcomes. All biomarkers were associated with large-for-gestational age (LGA) status (OR 1.61, P<0.001; OR 1.45, P<0.001; OR 3.62, P=0.032 for glycated albumin, fructosamine, and HbA1c, respectively). All had similar AUC for at least one neonatal complication (0.82; 0.81; 0.79, respectively). For newborn respiratory disorders, AUCs were 0.83, 0.81, and 0.76, respectively, and for LGA status were 0.81, 0.79, and 0.71, respectively.

Conclusion: Raised values of glycated albumin and fructosamine were associated with particular perinatal complications in newborns of mothers with GDM, better discriminating mothers of newborns with and without complications than HbA1c.

Keywords
Biomarkers; Fructosamine; Gestational diabetes mellitus; Glycated albumin; Glycemic markers; Hemoglobin A1c

1 | INTRODUCTION

Strict glycemic control is the cornerstone in reducing perinatal complications of the offspring of diabetic mothers.¹ This cannot be achieved without reliable glycemic markers during pregnancy, as self-monitoring blood glucose reflects only instantaneous blood glucose levels. The current gold standard for indicator of glycemic control among patients with diabetes mellitus is hemoglobin A1c (HbA1c).
its association with adverse pregnancy outcomes has been previously reported. However, its use as a suitable marker during pregnancy has been increasingly questioned: HbA1c reflects average glycemia over the preceding 2–3 months (a long time frame) and appears to be affected by iron deficient states.

Several authors suggest glycated albumin as a favorable alternative. It gives information regarding the previous 2–3 weeks, it is not affected by hemoglobin metabolism or iron deficient states, and it changes rapidly and markedly. It has also recently been reported that, in GDM, glycated albumin is less affected than HbA1c by insulin resistance and diastolic blood pressure. Few studies exist that investigate the association between glycated albumin in diabetic mothers and complications in their children, and these studies have conflicting results.

Another shorter-term glycemic marker of interest is fructosamine. It provides information over the preceding 2–4 weeks and it gives a rapid and precise measurement. Its current applicability is limited to populations where HbA1c is thought to be an inaccurate indicator of glycemia. Very few studies to date have evaluated its association with neonatal outcomes, and results are inconsistent.

The aim of the present study was to assess the clinical utility of glycated albumin and fructosamine in women with GDM by exploring the potential association between these biomarkers and neonatal complications.

2 MATERIALS AND METHODS

The present study took place in the Department of Maternal-Fetal Medicine of Central Lisbon Hospital Center, a Portuguese obstetric referral center, which offered a program providing comprehensive education and care for pregnant women with GDM. Screening for GDM is universal among pregnant women in Portugal and prenatal care is free. Diagnosis of GDM is based on the criteria of the International Association of Diabetes and Pregnancy Study Groups. Goals for treatment in the study center were: fasting glucose <5.3 mmol/L (<95 mg/dL) and 1-hour postprandial glucose <7.8 mmol/L (<140 mg/dL).

In the present prospective single-center cohort study, a convenience sample of women with GDM and singleton pregnancies who attended the clinic between November 21, 2016, and September 4, 2017, were recruited. Exclusion criteria were thyroid dysfunction, steroid use, and nephrotic syndrome, all of which can affect albumin metabolism. Data were collected throughout pregnancy and up to the 8th week after delivery. The study received approval from the ethical committees and review boards of Central Lisbon Hospital Center, APDP-Diabetes Portugal, NOVA Medical School, and National Committee of Data Protection. Written informed consent was obtained from all participants.

Total albumin values were determined by the bromocresol green method. Glycated albumin (%) was obtained using the conversion equation:

\[
\%\text{Glycated albumin} = \frac{\text{GSP}(\mu\text{mol/L}) \times 0.182 + 1.97}{\text{Total albumin}(\text{g/dL})} + 2.9.
\]

Fructosamine was measured by Diazyme Glycated Serum Protein Assay. Using this method, protein fragments or amino acids, glucose and \(H_2O_2\) are generated, and the \(H_2O_2\) measured by a colorimetric Trinder end-point reaction. The absorbance generated at 546–600 nm is proportional to the concentration of glycated serum proteins.

HbA1c (%) was measured by high-performance liquid chromatography with boronate affinity. HbA1c was estimated as the National Glycated Hemoglobin Standard Program (NGSP) equivalent value and the estimated Internal Federation of Clinical Chemistry (IFCC) equivalent value using the following equation:

The manufactures of the reagents used for the determination of glycated albumin, fructosamine and HbA1c were Beckman Coulter, Inc. (Brea, CA, USA), Diazyme Laboratories (Poway, CA, USA) and Trinity Biotech/Menarini Diagnostics (Bray, Ireland), respectively.

Data were retrieved on mother’s age and ethnicity, parity, history of diabetes in first degree relatives, pre-pregnancy body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters), history of hypertensive disorders of pregnancy, smoking status, timing of GDM diagnosis (during 1st/2nd trimesters), treatment modality, mode of delivery, gestational age at delivery, and infant’s birthweight. HbA1c, glycated albumin, and fructosamine levels were measured simultaneously, every 4 weeks, after the inclusion of each participant. The measurements used in the final analysis were those temporally closer to the date of birth. All newborns were checked for complications defined as: hypoglycemia (blood glucose <1.9 mmol/L); respiratory disorders (infants requiring oxygen therapy); hypocalcemia (serum calcium levels <2.0 mmol/L); polycythemia (peripheral venous serum hematocrit levels >65% [0.65/L]); hyperbilirubinemia (infants requiring phototherapy); large-for-date status (birthweight >90th percentile for gestational age); myocardial hypertrophy (intraventricular septum thickness >5 mm on ultrasonography); and admission to the neonatal care unit (pediatricians decided there was a need for surveillance in the intermediate/intensive care unit).

Categorical data were presented as frequencies (percentages), and quantitative variables as mean and standard deviation (SD)/(min, max). First, it was analyzed whether any of the aforementioned factors were associated with at least one complication. Second, the mean values of the biomarkers were compared between the two groups of infants for each particular complication. Third, multivariable logistic regression models were used to assess the association of HbA1c, glycated albumin, and fructosamine with at least one complication, and with the particular complications that had significantly different mean values of the glycemic markers between the two groups. In these analyses, clinical models were obtained, and the added value of each of the biomarkers to each of these models was quantified by the areas under the receiver operating characteristic curve (AUC). A P value of <0.05 was considered statistically significant. Statistical analyses were performed with R (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria).
RESULTS

Among the 100 enrolled women, 15 were excluded owing to hypo-
thyroidism (n=10), hyperthyroidism (n=2), steroid use (n=2), and
nephrotic syndrome (n=1). Therefore, 85 women were included in the
final analysis.

Baseline characteristics of the study participants (with and with-
out complications) are shown in Table 1. Features that differed signifi-
cantly between the two groups were: mean gestational age at birth
with 37 (SD 2.6) vs 39 (SD 0.8) weeks (P=0.006); rate of cesarean
delivery (44.7% vs 23.7%, P=0.047); mean glycated albumin level
with 12.1 (SD 18.9) vs 10.7 (18.3) % (P=0.024); and mean fructosamine with
165.8 (81.3) vs 137.8 (48.5) µmol/L (P=0.049). There was at least
one complication in 47 newborns: 25 (29.4%) were admitted to the
neonatal care unit; 24 (28.2%) had hyperbilirubinemia (all improved
following phototherapy); 24 (28.2%) had hypoglycemia (none with
convulsions); 21 (24.7%) had respiratory disorders (four required ven-
tilator management because of respiratory distress syndrome); 11
(12.9%) were large-for-date; two (2.4%) had myocardial hypertrophy
(none associated with heart failure); and two (2.4%) had hypocalcemia.
There were no detected cases of polycythemia. Thirty-one neonates
had more than one complication.

Table 2 compares mothers’ biomarkers between newborns with and
without complications. For respiratory disorders and large-for-date sta-
tus, glycated albumin differed significantly between mothers of neonates
with and without these complications (mean=13.2% vs mean=10.9%,
P=0.002; mean=14.8% vs mean=11.0%, P<0.001, respectively).
Regarding glycated albumin, no other differences were found.
Fructosamine also only differed significantly between the mothers of
newborns with respiratory disorders (mean=187.3 µmol/L vs mean=141.9 µmol/L, P=0.007), and with and without LGA newborns
(mean=228.5 µmol/L vs mean=141.9 µmol/L, P<0.001).
HbA1c was only significantly different between the mothers of
neonates who were LGA and the mothers of those who were not
(mean=5.4% vs mean=5.0%, P=0.032).

In the univariable analysis for the outcome presence of at least
one complication, gestational age at birth (OR: 0.51, 95% CI 0.32–
0.83, P=0.006), family history of diabetes (OR: 2.30, 95% CI 0.94–5.6,
P=0.069), cesarean delivery (OR: 2.60, 95% CI 1.01–6.69, P=0.047), and timing of GDM diagnosis (OR: 0.48, 95% CI 0.20–1.16, P=0.047). Gestational age at birth, family history of diabetes, and cesarean delivery were selected as candidates to the multivariable clinical model. Table 3 summarizes the multivariable regression models for this outcome. Gestational age at birth, family history of diabetes, and cesarean delivery remained in the clinical model. After adjusting for these variables, all the studied biomarkers, except HbA1c, were significantly associated with having at least one neonatal complication: for each additional unit of glycated albumin and for each 20 units increase of fructosamine, there was a 33% and 24% increase in the odds of a newborn having this outcome, respectively. The model with glycated albumin had the highest AUC (0.82, 95% CI 0.73–0.91), followed closely by fructosamine (0.81, 95% CI 0.72–0.91) and then by HbA1c (0.79, 95% CI 0.69–0.89).

Gestational age at birth (OR: 0.69, 95% CI 0.52–0.92, P=0.010), mother’s age (OR: 1.11, 95% CI 1.01–1.22, P=0.025), and treatment modality (OR: 2.92, 95% CI 1.04–8.23, P=0.042) were selected as candidates to the clinical multivariable model of the outcome respiratory disorders. The final multivariable regression results (Table 4), after adjusting by the two variables that remained in the clinical model (gestational age at birth and mother’s age), showed that for each additional unit of glycated albumin and for each 20 units increase in fructosamine, there was a 41% and 26% increase in the odds of a newborn having a respiratory disorder at birth, respectively. Again, only HbA1c was not significantly associated with this outcome. The discriminative ability of the model with glycated albumin regarding this disorder (AUC=0.83, 95% CI 0.73–0.94) was higher than that of fructosamine (AUC=0.81, 95% CI 0.71–0.92) and both these markers seem to perform better than HbA1c (AUC=0.76, 95% CI 0.63–0.89).

In the univariable analysis for the outcome LGA, GDM diagnosed during the 2nd trimester (OR: 0.26, 95% CI 0.06–1.07, P=0.062) was selected as candidate to the multivariable study, as well as gestational age at GDM diagnosis, parity, smoking status, and pre-pregnancy BMI by their known association with birth weight. However, no multivariable model was obtained. Nevertheless, raised values of all biomarkers were associated with an increase in the odds of having a newborn that was LGA: for each additional unit of glycated albumin, there was a 61% increase (OR: 1.61, 95% CI 1.24–2.10, P<0.001); for each 20 units of fructosamine, there was an increment of 45% (OR: 1.45, 95% CI 1.19–1.78, P<0.001); and for each additional unit of HbA1c, an approximately 4-fold increase was obtained (OR: 3.62, 95% CI 1.12–11.69, P=0.032). Once again, glycated albumin had the highest AUC (0.81, 95% CI 0.65–0.97) followed by fructosamine (0.79, 95% CI 0.63–0.95) and HbA1c (0.71, 95% CI 0.56–0.86).

### DISCUSSION

In the present prospective cohort study, and contrary to HbA1c, maternal glycated albumin was an independent predictor of the presence of at least one neonatal complication, and specifically of respiratory adverse events.
disorders. In fact, for each additional unit of glycated albumin, the odds of newborns of mothers with GDM having at least one neonatal complication was 33% higher, and of having a respiratory disorder was 45% higher. Glycated albumin also differed for LGA neonates and showed no association with the remaining complications.

The case–control studies conducted by Sugawara et al. in 2016 (involving 42 pregnant diabetic women) and then in 2017 (with 71 women with diabetic pregnancies) both concluded that glycated albumin was useful for considering more newborn complications, namely respiratory disorders, hypoglycemia, hypocalcemia, myocardial hypertrophy, and LGA status. Nevertheless, the present study differed from the two mentioned above as it exclusively comprised women with GDM as opposed to retrospective studies that included pregnant women with type 1 diabetes, type 2 diabetes, and GDM. This may be a key methodological difference because pre-existing diabetes possibly represents a more marked carbohydrate intolerance than GDM in the spectrum of glycemic dysfunctions of pregnancy with different diseases having distinct clinical implications. Homogeneous populations can also be influenced by factors that may interfere with glycemic indicators. In Portugal, for instance, supplementation of iron is mandatory as early as 20 weeks of gestation, which is contrary to the management in Japan. Hashimoto et al. already showed that HbA1c is affected by iron-deficiency states in late pregnancy and glycated albumin is not, however the impact of iron supplementation remains unknown. Li et al. conducted a case–control study involving 2118 Chinese women (639 with GDM) which found that the risk of birth weight ≥3500 g, and the risk of macrosomia, increased significantly with glycated albumin levels ≥12% at 24–28 weeks of pregnancy, and ≥15% at 36–38 weeks of pregnancy, and with glycated albumin levels ≥15% at 24–28 weeks of pregnancy, and ≥20% at 36–38 weeks of pregnancy. The Japan Glycated Albumin Study Group, in 2012 proposed 4.5%–5.7% and 11.5%–15.7% as reference intervals for HbA1c and glycated albumin in pregnant women, and the risk of macrosomia increased significantly with glycated albumin levels ≥15% at 24–28 weeks of pregnancy.

There are only a few research studies focused on the utility of fructosamine in GDM. Nevertheless, this is seen as significant, particularly in countries such as Portugal where the measurement of glycated albumin is unavailable in many clinical settings. The measurement and interpretation of fructosamine is relatively inexpensive and technically simple. In fact, in the present study, raised values of maternal fructosamine (and also glycated albumin) were associated with three outcomes: (1) having at least one neonatal complication; (2) having respiratory disorder; and (3) having LGA status. In a prospective cohort including 41 pregnant women with diabetes (27 with GDM) undertaken by Delgado et al., no association was demonstrated between fructosamine and macrosomia, as reference intervals for HbA1c and glycated albumin were associated with three outcomes: (1) having at least one neonatal complication; (2) having respiratory disorder; and (3) having LGA status. In the present study, HbA1c value was associated with large-for-date status. These results seem to concur with those reported by Gandhi and colleagues, even though this study differs from the referred study, namely in the criteria used to identify GDM, and in the clinical approach to women with GDM. In the present investigation, large-for-date status was defined as birth weight ≥90th percentile for Gestational age, as reported by the National Center for Health Statistics. In the present study, large-for-date status was defined as birth weight ≥90th percentile for Gestational age, as reported by the National Center for Health Statistics. In the present study, large-for-date status was defined as birth weight ≥90th percentile for Gestational age, as reported by the National Center for Health Statistics. In the present study, large-for-date status was defined as birth weight ≥90th percentile for Gestational age, as reported by the National Center for Health Statistics. In the present study, large-for-date status was defined as birth weight ≥90th percentile for Gestational age, as reported by the National Center for Health Statistics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Clinical model</th>
<th>Clinical model + GA</th>
<th>Clinical model + fructosamine</th>
<th>Clinical model + HbA1c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Gestational age at delivery, wk</td>
<td>0.46 (0.26–0.79)</td>
<td>0.005</td>
<td>0.39 (0.21–0.72)</td>
<td>0.002</td>
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<td>Family history of diabetes</td>
<td>2.96 (1.06–8.25)</td>
<td>0.038</td>
<td>3.05 (1.03–9.04)</td>
<td>0.044</td>
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<tr>
<td>Cesarean delivery</td>
<td>3.13 (1.05–9.29)</td>
<td>0.040</td>
<td>3.19 (1.03–9.84)</td>
<td>0.044</td>
</tr>
<tr>
<td>Glycated albumin, %</td>
<td>1.33 (1.06–1.68)</td>
<td>0.015</td>
<td>1.24 (1.02–1.49)</td>
<td>0.027</td>
</tr>
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<td>Fructosamine, µmol/L</td>
<td>1.24 (0.26–0.79)</td>
<td>0.005</td>
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<td>HbA1c, %</td>
<td>1.33 (1.06–1.68)</td>
<td>0.015</td>
<td>1.24 (1.02–1.49)</td>
<td>0.027</td>
</tr>
</tbody>
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Abbreviations: CI, confidence interval; GA, glycated albumin; HbA1c, glycated hemoglobin; OR, odds ratio.

For each 20 units increase in fructosamine.
however, and contrary to what was found with glycated albumin and fructosamine, HbA1c only showed association with large-for-date status. Arumugam et al. reported HbA1c concentration in late pregnancy (36–38 weeks) to be a good predictor of neonatal hypoglycemia in pregnant women with overt diabetes and GDM. In a similar study, Kline et al. showed that HbA1c >6.5% in the 3rd trimester had a stronger association with neonatal care unit admission and intravenous glucose requirement.

In the present study sample, the performance of glycated albumin and fructosamine as predictive factors of at least one neonatal complication and of respiratory disorders in infants of mothers with GDM was quite similar. They were also similar in their association with LGA newborns. Glycated albumin and fructosamine performed better than HbA1c for these purposes.

In the present study cohort, the studied biomarkers did not differ significantly between the two groups of women under study for the majority of complications. The authors hypothesize this result was obtained because (1) it was a small sample size study; (2) it was a single-center study that had a diabetes program with aggressive glycemic goals consequently resulting in low mean biomarker values. It is also accepted by the authors that other important factors could have been considered. For instance, in the case of GDM, additional measures of fetal growth and adiposity (which could be better measured by infant body composition) should be considered, as they are more closely associated with glycemic markers than with birth weight alone.

In the present study, glycated albumin and fructosamine, two promising short-term glycemic markers in diabetic pregnancy, proved their usefulness in predicting perinatal complications in the offspring of mothers with GDM. Both showed a higher discriminative ability over HbA1c for this purpose. Nevertheless, GDM is not a homogeneous dysglycemic condition. As a result, these markers may not have the same utility in all GDM cases. Additionally, although in the present study no associations were identified between the biomarkers and ethnicity, ethnic differences have been reported for both HbA1c and glycated albumin. Accordingly, multicenter, ethnically diverse prospective studies with large numbers of patients are needed to establish the current utility of these alternative biomarkers in GDM.

**TABLE 4 Multivariable regression model for presence of a neonatal respiratory disorder.**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Clinical model</th>
<th>Clinical model + GA</th>
<th>Clinical model + fructosamine</th>
<th>Clinical model + HbA1c</th>
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<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Gestational age at delivery, wk</td>
<td>0.67 (0.50–0.90)</td>
<td>0.007</td>
<td>0.63 (0.43–0.93)</td>
<td>0.020</td>
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<tr>
<td>Mother’s age, y</td>
<td>1.13 (1.02–1.25)</td>
<td>0.018</td>
<td>1.15 (1.02–1.30)</td>
<td>0.018</td>
</tr>
<tr>
<td>Glycated albumin, %</td>
<td>1.41 (1.11–1.78)</td>
<td>0.004</td>
<td>1.41 (1.11–1.78)</td>
<td>0.004</td>
</tr>
<tr>
<td>Fructosamine, µmol/L&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.26 (1.05–1.50)</td>
<td>0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>2.28 (0.79–6.59)</td>
<td>0.129</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; GA, glycated albumin; HbA1c, glycated hemoglobin; OR, odds ratio.

<sup>a</sup>For each 20 units increase in fructosamine.

**AUTHOR CONTRIBUTIONS**

NM contributed to the conception and design of the study, interpretation and analysis of the data, and writing the manuscript. FS and RTR contributed to the design of the study. ALP contributed to the design of the study, and interpretation and analysis of the data. RA contributed to the collection of the data. MA contributed to the interpretation and analysis of the data. All authors contributed to revising the manuscript.

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**CONFLICTS OF INTEREST**

The authors have no conflicts of interest.

**REFERENCES**


