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► To cite this version:

P. Poupon, N. Foussard, Catherine Helmer, Audrey Cougnard-Gregoire, Kalina Rajaobelina, et al.. Serum fructosamine predicts macrosomia in well-controlled hyperglycaemic pregnant women: an observational cross-sectional study. *Diabetes & Metabolism*, In press, 46 (3), pp.219-222. <10.1016/j.diabet.2019.07.003>. <hal-03139029>

HAL Id: hal-03139029

<https://hal.science/hal-03139029v1>

Submitted on 22 Aug 2022

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Serum fructosamine predicts macrosomia in well-controlled hyperglycaemic pregnant women: an observational cross-sectional study

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Received 27 January 2019; Accepted 7 July 2019-07-08

Abstract

Aim. – While serum fructosamine may be a good marker of glucose control in pregnant women with diabetes, its relationship with macrosomia is still uncertain.

Methods. – In 130 hyperglycaemic women with singleton pregnancies (117 gestational diabetes mellitus, 13 pregestational diabetes), serum fructosamine and HbA1c levels were measured at 25 ± 7 weeks of gestation. Levels in mothers of infants with and without macrosomic newborns (birth weight > 4000 g and/or large-for-gestational-age birth weight > 90 th percentile) were compared using logistic regression analysis adjusted for macrosomia risk factors.

Results. – These 130 pregnant women were 33 ± 5 years old; their BMI before pregnancy was 27.7 ± 6.9 kg/m², and they gained 7.5 ± 5.1 kg during the first 6 months of gestation. Glucose control was good according to HbA1c levels ($5.3 \pm 0.3\%$; 34 ± 2 mmol/mol), yet 17/130 (13%) newborns had macrosomia: 3900 ± 227 g vs 3057 ± 512 g ($P < 0.001$) in the others. These mothers were older and had higher parity, whereas their BMI scores before pregnancy and gestational weight gains did not differ. Fructosamine levels were also higher at 221 ± 40 μ mol/L vs 192 ± 22 μ mol/L ($P < 0.001$), respectively, and remained significant even after adjusting for maternal age, BMI, parity, type of diabetes, antecedents of macrosomia and excessive gestational weight gain. By contrast, HbA1c did not differ between the two groups. In fact, nearly two-thirds (64.7%) of the mothers of macrosomic newborns had fructosamine levels > 200 μ mol/L vs 31.9% of mothers with non-macrosomic newborns ($P < 0.05$).

Conclusion. – High fructosamine levels are associated with macrosomia in the newborns of well-controlled hyperglycaemic pregnant women.

Keywords: Diabetes; Fructosamine; HbA1c; Macrosomia; Pregnancy

Introduction

Glucose control reduces birth weight in the offspring of mothers with gestational diabetes mellitus (GDM) [1] and, for women with pregestational diabetes, HbA1c levels < 6% (42 mmol/mol) are necessary to prevent macrosomia [2]. Recent studies, however, continue to report high rates of macrosomia, at around 15% for GDM [3] and up to 50% for type 1 diabetes (T1D) [4]. Such high rates may result from non-glucose-related mechanisms, such as excess lipid substrates in pregnant women with obesity [5] or excessive gestational weight gain [6]. Nevertheless, even moderately high glucose levels can contribute to fetal overgrowth in 'well-controlled' diabetes if they arise early in pregnancy [7] or are within the higher range of recommended levels of glucose [8].

HbA1c can be used as a secondary marker of glucose control in pregnancy [9]. However, it is imperfect because it is influenced by the iron deficiency of pregnancy and is not the best predictor of birth weight, according to the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study [10]. In addition, other parameters, such as glycated proteins, may be more relevant in pregnant women due to their shorter half-life and because they are not influenced by changes in haemoglobin turnover or iron metabolism [11]. Yet, their superiority over HbA1c continues to be debated [12].

Thus, our hypothesis was that fructosamine measured during the third trimester of pregnancy might be better at predicting macrosomia than HbA1c. In addition, to determine the value of serum fructosamine *vs* HbA1c as a marker of glycaemic control during diabetic pregnancy, the relationship of these two markers with macrosomia was also analyzed.

Subjects and methods

For our present single-centre, observational, cross-sectional study, consecutive pregnant women with pregestational diabetes or GDM, referred to the Nutrition–Diabetology unit of the University Hospital Haut-Lévêque (Bordeaux, France) during 2013–2015 at 25 ± 7 weeks of amenorrhea, were prospectively included. Inclusion criteria were gestational or pregestational diabetes (type 1 or 2) with a singleton pregnancy in progress, whereas the only exclusion criteria were age < 18 years and non-affiliation to social security.

The study protocol was approved by the local ethics committee, and all of these women provided their written informed consent to participate.

Clinical data

Age, weight and body mass index (BMI) before pregnancy were registered along with other risk factors for GDM: familial history of diabetes; previous personal history of GDM; and/or macrosomia for non-nulliparous women. As for the newborns, their birth weights and percentiles according to gestational age were recorded. Macrosomia was defined as a birth weight ≥ 4000 g and/or large-for-gestational-age birth weight $\geq 90^{\text{th}}$ percentile.

Biological data

For GDM, the diagnostic strategy at our centre is based on recommendations of the French Diabetes Society [14]. Screening for GDM was performed in women with risk factors: maternal age ≥ 35 years; BMI ≥ 25 kg/m²; first-degree family history of diabetes; personal history of gestational diabetes; and macrosomic newborns. The diagnosis was based on fasting plasma glucose (FPG) levels before 24 weeks of gestation (early GDM if FPG ≥ 5.10 mmol/L) or an abnormal 75-g oral glucose tolerance test (OGTT) performed at weeks 24–28 of gestation (late GDM if glycaemia at 0 h ≥ 5.10 mmol/L, at 1 h ≥ 10 mmol/L and/or at 2 h ≥ 8.5 mmol/L). FPG and OGTT were not assessed in women with preexisting diabetes.

All participants were also asked to undergo blood sampling the week before or after their first visit to our centre for HbA1c (using high-performance liquid chromatography) and fructosamine (nitroblue tetrazolium coloration assay) measurements. The blood test was performed on average at 25 ± 7 weeks of gestation.

Statistical analysis

Differences between the mothers of macrosomic vs non-macrosomic newborns were tested using Student's test for continuous variables and chi-squared test for categorical variables, or Fisher's test when sample-size conditions were not met. The relationship between serum fructosamine and macrosomia was tested by logistic regression analysis, adjusted for other risk factors of macrosomia: maternal age; BMI; excessive gestational weight gain; antecedents of macrosomia; parity; and type of diabetes (pregestational, early or late GDM). A *P* value < 0.05 was considered significant. The relationship between HbA1c and macrosomia was also tested, applying the same adjustments. In addition, a receiver operating characteristic (ROC) curve was established to determine the sensitivity and specificity of fructosamine and of HbA1c for predicting macrosomia, using a threshold determined by the Youden index.

Results

Characteristics of the study population

Our 130 pregnant women were 33 ± 5 years old; their BMI before pregnancy was 27.7 ± 6.9 kg/m² and they gained 7.6 ± 5.1 kg during the first 6 months of gestation. Of these women, 13 (10%) had pregestational diabetes [10 (7.7%) T1D, 3 (2.3%) type 2 diabetes (T2D)], while 44 (33.8%) had early GDM and 73 (56.2%) had late GDM. T1D women were aged 31.0 ± 3.9 years; their average duration of diabetes was 14.8 ± 3.5 years and their average BMI was 25.2 ± 5.2 kg/m². As expected, T2D women were older (38.0 ± 4.3 years) and heavier (BMI: 39.0 ± 1.5 kg/m²), and their average duration of diabetes was 10.7 ± 4.0 years.

Mothers with macrosomic vs non-macrosomic newborns

Overall, 17 (13%) newborns had macrosomia, whereas the rate of macrosomic babies was 11.8% in women with GDM and 20% in women with pregestational diabetes. Gestational age at birth (37 ± 2 weeks) did not differ between the two groups.

As depicted in [Table I](#), the mothers of macrosomic newborns were older and had higher parity, but did not significantly differ by either BMI or gestational weight gain. HbA1c also did not differ between the two groups. However, fructosamine levels were 15% higher in the mothers with large babies: 221 ± 40 μmol/L vs 192 ± 22 μmol/L ($P < 0.001$) in the others.

Relationship between fructosamine and macrosomia

According to logistic regression analysis, the association between serum fructosamine (μmol/L) and presence of macrosomia remained significant [odds ratio (OR): 1.05, 95% confidence interval (CI): 1.01–1.09; $P = 0.009$] even after adjusting for maternal age, BMI, parity, antecedents of macrosomia, excessive gestational weight gain and type of diabetes (pregestational or GDM; [Table II](#)). On the other hand, there was no significant association between HbA1c and macrosomia when using the same adjustments (OR: 1.31, 95% CI: 0.31–5.50; $P = 0.715$; [Table III](#)).

Thus, as illustrated in [Fig. 1](#), fructosamine was more efficient than HbA1c in predicting macrosomia, with an area under the ROC curve (AUROC) of 0.73 (95% CI: 0.58–0.86) vs 0.58 (95% CI: 0.44–0.72) for HbA1c. The threshold for optimal sensitivity and specificity of fructosamine was 200 μmol/L, with a sensitivity of 64.7% and specificity of 68.1%. Moreover, the rate of women with fructosamine levels > 200 μmol/L was significantly higher in women who delivered macrosomic newborns: 64.7% vs 31.9% ($P < 0.05$).

Sensitivity analysis: Fructosamine and macrosomia in women with GDM (n = 117)

Thirteen newborns (11.8%) of mothers with GDM had macrosomia: their mean birth weight was 3968 ± 205 g vs 3081 ± 483 g in non-macrosomic newborns ($P < 0.000$). These mothers were older (36 ± 4 years vs 33 ± 5 years; $P = 0.01$) and had higher parity (1.4 ± 1.1 vs 0.6 ± 0.9 ; $P = 0.004$). HbA1c levels, however, did not differ significantly ($5.1 \pm 0.2\%$ vs $5.2 \pm 0.4\%$; $P = 0.70$), whereas fructosamine levels were higher: 205 ± 22 $\mu\text{mol/L}$ vs 191 ± 19 $\mu\text{mol/L}$ ($P = 0.016$).

Nevertheless, the association between serum fructosamine and macrosomia did not reach significance after adjusting for maternal age, parity, antecedents of macrosomia and excessive gestational weight gain (OR: 1.05, 95% CI: 0.99–1.11; $P = 0.10$). In addition, HbA1c and macrosomia were not associated, using these same adjustments (OR: 1.01, 95% CI: 0.10–9.78; $P = 0.99$).

Discussion

Numerous studies have reported a relationship between HbA1c at mid-pregnancy and birth weight in hyperglycaemic pregnant women. In those with pregestational diabetes, however, these studies reported HbA1c levels of around 6% (42 mmol/mol) in T1D mothers [2,4,8] and 5.7% (39 mmol/mol) in T2D mothers [4] of infants with macrosomia, which are rates higher than in our study patients. For GDM, rates of macrosomia were significantly higher only in women with HbA1c $\geq 6\%$ (42 mmol/mol), representing $< 10\%$ of the studied population [13]. In the HAPO Study, mean HbA1c was $4.8 \pm 0.4\%$ (29 ± 2.4 mmol/mol), which was related to the birth of a large-for-gestational-age infant, although this relationship was weaker than for any glucose level, thereby leading to the conclusion that HbA1c is not an alternative for GDM diagnosis [10]. Fructosamine was not tested in these studies.

The relationship between maternal serum fructosamine and macrosomia in newborns has been previously tested in a few studies. However, it was not significant in the 301 high-risk pregnant women studied by Cahill et al. [14], where two-thirds of the participants had pregestational diabetes and only one-third had HbA1c levels $< 6\%$ (42 mmol/mol). In the general obstetric population, Schrader et al. [15] found that glycated protein improved the prediction of macrosomia based on fasting glucose levels. Due to its shorter half-life, fructosamine may be better adapted than HbA1c for detecting the effects of intervention: in non-diabetic pregnant women (HbA1c: 4.9%, 30 mmol/mol), low or moderate glycaemic index (GI) diets led to a significant reduction in fructosamine, whereas HbA1c was not

decreased [16]. Because of iron deficiency, HbA1c increases in late pregnancy independently of glucose control, which does not occur with either glycated albumin or fructosamine [17].

The relationship detected in our present study between serum fructosamine and macrosomia was significant after adjusting for the main predictors of macrosomia, and the fructosamine threshold of 200 $\mu\text{mol/L}$ may be a useful indicator in clinical practice.

Our study has some limitations. The number of participants was limited, which may explain why the association between fructosamine and macrosomia failed to reach significance in the GDM subgroup. Nevertheless, thresholds must now surely be proposed with caution in cases of GDM, as the relationship between markers of glucose exposure and outcome for neonates is a continuum [20], whereas the fructosamine threshold of 200 $\mu\text{mol/L}$ may well be an indicator of macrosomia risk in clinical practice.

Conclusion

Maternal fructosamine levels were associated with macrosomia in the newborns of pregnant women with ‘well-controlled’ diabetes according to their HbA1c levels, and the relationship between fructosamine and macrosomia remained significant even after adjusting for maternal age, BMI, parity, type of diabetes, antecedents of macrosomia and excessive gestational weight gain. Thus, such an analysis could be helpful for predicting macrosomia in pregnant women with ‘well-controlled’ diabetes.

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Figure legend

Fig. 1. Receiver operating characteristic (ROC) curves for the prediction of macrosomia according to fructosamine vs HbA1c.

Figure 1: ROC Curve for the prediction of macrosomia according to fructosamine and HbA1c.

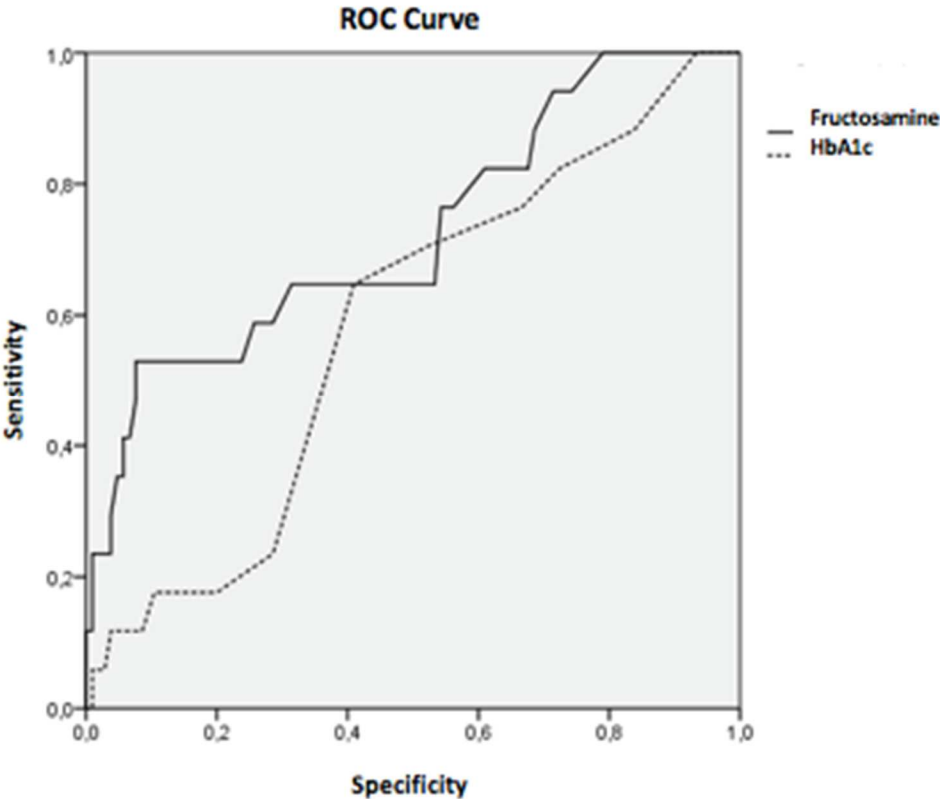


Table I: comparison between mothers of macrosomic vs non macrosomic new-borns

	Non macrosomic	Macrosomic	<i>P</i>
N	113	17	
Birth weight (g)	3057 ± 512	3900 ± 227	< 0.000
Birth weight centile according to gestational age (ctile)	45 ± 25	92 ± 5	< 0.000
Age of Mother (yrs)	33 ± 5	35 ± 4	0.048
BMI before pregnancy (kg/m ²)	27.6 ± 7.0	28.8 ± 5.5	0.505
Excessive Gestational Weight Gain (%)	31.1	35.7	0.729
Parity (number of previous children)	0.6± 0.9	1.4 ± 1.0	< 0.005
HbA1c (% ; mmol/mol)	5.2±0.5 ; 33±3.2	5.3±0.2 ; 34±1.3	0.289
Fructosamine (µmol/L)	192 ± 22	221 ± 40	< 0.000
Type of diabetes: GDM (n ; %) Early GDM (n ; %) Pre-gestational (n , %)	n= 68; 60.2% n= 36; 31.9% n= 9; 8%	n= 5; 29.4% n= 8; 47.1% n= 4; 23.5%	0.029

Table II: Logistic regression testing relationship between fructosamine and macrosomia

<i>Variables</i>	<i>Odd Ratio</i>	<i>IC 95%</i>	<i>P value</i>
Fructosamine ($\mu\text{mol/l}$)	1.05	1.01-1.09	$P = 0.009$
Age (years)	1.11	0.93-1.31	$P = 0.237$
BMI (kg/m^2)	1.06	0.93-1.20	$P = 0.398$
Parity (number)	1.18	0.53-2.60	$P = 0.687$
Pregestational diabetes (Yes)	0.55	0.15-2.02	$P = 0.366$
Previous macrosomia (Yes)	21.39	2.45-186.69	$P = 0.006$
Excessive GWG (Yes)	2.53	0.52-12.37	$P = 0.252$

Table III: Logistic regression testing relationship between HbA1c and macrosomia

<i>Variables</i>	<i>Odd Ratio</i>	<i>IC 95%</i>	<i>P value</i>
HbA1c (%)	1.31	0.31-5.50	<i>P</i> = 0.715
Age (years)	1.13	0.95-1.35	<i>P</i> = 0.165
BMI (kg/m ²)	0.99	0.88-1.11	<i>P</i> = 0.93
Parity (number)	1.04	0.47-2.31	<i>P</i> = 0.918
Pregestational diabetes (Yes)	1.94	0.66-5.74	<i>P</i> = 0.230
Previous macrosomia (Yes)	48.50	5.16-456.01	<i>P</i> = 0.001
Excessive GWG (Yes)	1.31	0.31-5.50	<i>P</i> = 0.715