



Skin Autofluorescence of Pregnant Women With Diabetes Predicts the Macrosomia of Their Children

Ninon Foussard,¹ Audrey Cougnard-Grégoire,² Kalina Rajaobelina,² Cécile Delcourt,² Catherine Helmer,² Thierry Lamireau,² Concepcion Gonzalez,¹ Virginie Grouthier,¹ Magalie Haissaguerre,¹ Laurence Blanco,¹ Laure Alexandre,¹ Kamel Mohammedi,¹ and Vincent Rigalleau^{1,2}

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Advanced glycation end products (AGEs) accumulated during long-term hyperglycemia are involved in diabetes complications and can be estimated by skin autofluorescence (sAF). During pregnancy, hyperglycemia exposes women to the risk of having a macrosomic newborn. The aim of this study was to determine whether sAF of women with diabetes during a singleton pregnancy could predict macrosomia in their newborns. Using an AGE Reader, we measured the sAF at the first visit of 343 women who were referred to our diabetology department during years 2011–2015. Thirty-nine women had pregestational diabetes, 95 early gestational diabetes mellitus (GDM), and 209 late GDM. Macrosomia was defined as birth weight $\geq 4,000$ g and/or large for gestational age ≥ 90 th percentile. Forty-six newborns were macrosomic. Their mothers had 11% higher sAF compared with other mothers: 2.03 ± 0.30 arbitrary units (AUs) vs. 1.80 ± 0.34 ($P < 0.0001$). Using multivariate logistic regression, the relation between sAF and macrosomia was significant (odds ratio 4.13 for 1-AU increase of sAF [95% CI 1.46–11.71]) after adjusting for several potential confounders. This relation remained significant after further adjustment for HbA_{1c} (among 263 women with available HbA_{1c}) and for women with GDM only. sAF of pregnant women with diabetes, a marker of long-term hyperglycemic exposure, predicts macrosomia in their newborns.

Diabetes during pregnancy can be divided into two categories: known preexisting diabetes and gestational diabetes mellitus (GDM). GDM is defined as glucose intolerance with onset or first recognition during pregnancy (1). The American Diabetes Association considers that GDM represents $\sim 90\%$ of all pregnancies with diabetes (1).

Diabetes during pregnancy is associated with a significant risk of adverse perinatal outcomes (2), including fetal macrosomia. There is a continuous association between maternal glucose levels and birth weight (3). Macrosomia, defined as birth weight $\geq 4,000$ g or large for gestational age (LGA) ≥ 90 th percentile, is the most common morbidity, occurring in 15–45% of infants exposed to hyperglycemia (4). It is critical to identify the population at risk to reduce the incidence of fetal macrosomia.

Skin autofluorescence (sAF) is a noninvasive measure by optical spectroscopy, which correlates to the skin concentrations of advanced glycation end products (AGEs) (5). Because the generation of AGEs is accelerated by hyperglycemia, sAF is considered a marker of abnormal glucose metabolism. sAF may allow the early detection of abnormal glucose tolerance in subjects at risk for prediabetes and type 2 diabetes (T2D) better than fasting plasma glucose or hemoglobin A_{1c} (HbA_{1c}) (6). A high intrinsic fluorescence measure has been associated with dysglycemic status at the first and second trimesters in pregnant women (7), and we have reported that sAF was higher in women with pregestational diabetes than in women with GDM (8). It is not known, however, whether sAF in pregnant women with hyperglycemia may relate to macrosomia in their offspring.

In 2011–2015, we measured sAF at 26.4 ± 6.2 weeks of amenorrhea in 343 women with singleton pregnancies and diabetes (39 with pregestational diabetes and 304 with GDM). The association between sAF and macrosomia of the offspring was assessed using multiple logistic regression analysis, adjusting for the other risk factors for macrosomia.

¹Nutrition-Diabetology, CHU de Bordeaux, Hôpital Haut-Lévêque, Pessac, France
²University of Bordeaux, INSERM, Bordeaux Population Health Research Center, Team Lifelong Exposures Health and Aging, UMR 1219, Bordeaux, France

Corresponding author: Ninon Foussard, ninonfoussard@yahoo.fr

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RESEARCH DESIGN AND METHODS

Study Population

We consecutively included singleton pregnant women with diabetes who were referred to the Nutrition-Diabetology unit of the University Hospital Haut-Lévêque (Bordeaux, France) between 2011 and 2015, at 26.4 ± 6.2 weeks of amenorrhea. From November 2011 to November 2012, we included 131 women who participated in our previous study (8) and for whom the birth weights of the newborns were available. From 2013 to 2015, 212 more women were included, and the birth weights of their newborns were systematically registered. The screening and diagnostic criteria for GDM, the registered variables, and the management of diabetes during pregnancy were the same for both periods of recruitment. The study was approved by the local ethics committee, and each patient provided written informed consent to participate. The diagnosis of GDM was based on the guidelines of the French Diabetes Society (9). The screening of GDM was performed if maternal age was ≥ 35 years or BMI ≥ 25 kg/m², or if there was first-degree family history of diabetes or personal history of GDM or previous macrosomic newborn. Early GDM was diagnosed by fasting blood glucose at the first trimester ≥ 0.92 g/L and < 1.26 g/L, and late GDM was diagnosed by an oral glucose tolerance test with 75 g of glucose at 24–28 weeks of amenorrhea (0-h blood glucose ≥ 0.92 g/L, 1-h ≥ 1.80 g/L, or 2-h ≥ 1.53 g/L). Some women included in the study had known pregestational diabetes or were diagnosed during pregnancy by a fasting blood glucose at the first trimester ≥ 1.26 g/L.

The women with GDM were managed by lifestyle intervention and medical nutrition therapy and advised to perform self-monitoring of blood glucose. Insulin was introduced if the glycemic goals (preprandial < 0.95 g/L and postprandial < 1.20 g/L) were not obtained. For women with pregestational diabetes, the glycemic goals were the same.

Among the studied variables, sAF was the main explanatory variable and macrosomia was the dependent variable.

sAF Measurement

During the first visit to our center, the accumulation of AGEs was estimated from sAF measured at the forearm with the AGE Reader (DiagnOptics Technologies BV, Groningen, the Netherlands) and expressed as arbitrary units (AUs). sAF was calculated by an observer-independent automated analysis, by dividing the average light intensity of the emission spectrum (300–600 nm) by the average light intensity of the excitation spectrum (300–420 nm). The reproducibility is indicated by a mean coefficient of variation $\sim 5\%$. The measurement was performed at a normal skin site of the forearm, without scars, lichenification, or other abnormalities.

Macrosomia

The birth weights and delivery dates were collected by phone call or review of obstetrical records. Centiles according to gestational age were estimated from fetal morphometric

charts of the French Association des Utilisateurs de Dossiers Informatisés en Pédiatrie, Obstétrique et Gynécologie. Macrosomia was defined by birth weight $\geq 4,000$ g and/or LGA ≥ 90 th percentile.

Other Variables

The potential explanatory variables, collected during the first consultation, included maternal age, parity, pregestational BMI, type of diabetes (pregestational diabetes and early and late GDM), systolic blood pressure (SBP) and diastolic blood pressure (DBP) at inclusion (24.4 ± 6.2 weeks of gestation), family history of diabetes previous history of macrosomia, and HbA_{1c} measured by blood test (high-performance liquid chromatography) at inclusion. The sex of newborns was collected by phone call after delivery or review of obstetric records.

Statistical Analysis

The results are presented as means \pm SD for continuous variables and as numbers (percentages) for categorical variables. The relations between sAF (main explanatory variable) and macrosomia (dependent variable) as well as between potential confounders (age, SBP, DBP, weeks of amenorrhea at sAF measurement, pregestational BMI, type of diabetes [pregestational and early and late GDM], parity, family history of diabetes, sex of newborn, weeks of gestation at delivery, and previous history of macrosomia) were tested by univariate logistic regression analysis.

Multivariate logistic regression analyses adjusted on all of the variables (except previous history of macrosomia, which was included only in sensitivity analysis among women with parity ≥ 1) were then performed with macrosomia as a dependent variable. Supplementary analyses were also performed after defining macrosomia only by birth weight $\geq 4,000$ g and only by LGA.

Four sensitivity analyses were performed for the women with insulin therapy status available, GDM only, HbA_{1c} available (with inclusion of HbA_{1c} in the model), and parity ≥ 1 (including a previous history of macrosomia in the model).

A *P* value < 0.05 was considered significant. The associations were presented as odds ratios (ORs) and 95% CIs. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of the Population

A total of 343 women participated in the study. They were 33.30 ± 5.22 years old, their pregestational BMI was 27.00 ± 6.84 kg/m², and 160 were nulliparous. Thirty-nine women had pregestational diabetes (sAF measurement at 21.9 ± 8.2 weeks of gestation), 95 had early GDM (sAF measurement at 22.7 ± 7.2 weeks of gestation), and 209 had late GDM (sAF measurement at 29.0 ± 3.4 weeks of gestation; *P* < 0.001 vs. early GDM and pregestational diabetes). The birth weight was $3,225 \pm 530$ g, and 46 newborns were macrosomic (13.4%).

Comparison Between Mothers of Macrosomic Versus Nonmacrosomic Newborns

The comparison between mothers of macrosomic versus nonmacrosomic newborns is depicted in Table 1. The mothers of macrosomic newborns were 2 years older, they had a lower mean gestational age at the time of sAF measurement, their parity was higher, they had more frequent history of macrosomia during previous pregnancies, and pregestational diabetes was more represented among them. Familial history of diabetes, pregestational BMI, and blood pressure at inclusion were not associated with macrosomia. The mothers of macrosomic newborns had higher sAF than the other mothers: 2.03 ± 0.30 vs. 1.80 ± 0.34 AU ($P < 0.0001$). The relation between sAF and birth weight as a continuous variable was not significant ($P = 0.18$ for the whole population, $P = 0.20$ for women with GDM, and $P = 0.69$ for women with pregestational diabetes).

Relation Between sAF and Macrosomia: Whole Population

In multivariate logistic regression model adjusted for all of the covariables (Table 2), a higher sAF was associated with a significant increased risk of macrosomia (OR 4.13 for 1-AU increase [95% CI 1.46–11.71]). A higher parity,

pregestational diabetes, and having no familial history of diabetes were also associated with an increased risk of macrosomia.

Among the 46 macrosomic newborns, 24 were defined on LGA criteria alone, 3 on birth weight $\geq 4,000$ g alone, and 19 on both criteria. The relation between sAF and a macrosomic newborn defined as LGA ($n = 43$ macrosomic newborns) was significant (OR 4.19 [95% CI 1.44–12.17]) after full adjustment. The relation between sAF and a $\geq 4,000$ g newborn ($n = 22$ macrosomic newborns) did not reach significance (OR 2.35 [95% CI 0.54–10.26]) after these adjustments.

Sensitivity Analyses

After introducing the insulin therapy status in the multivariate model, higher sAF remained associated with an increased risk of macrosomia (OR 4.32 [95% CI 1.52–12.30]).

A total of 303 women had only GDM and not pregestational diabetes. In the sensitivity analysis performed in these women with GDM, sAF was related to macrosomia (OR 3.80 [95% CI 1.20–12.00]) after adjustment for previously mentioned confounders (Table 3).

HbA_{1c} was available for 275 women with a mean (SD) of $5.3 \pm 0.6\%$ or 35.0 ± 4.0 mmol/mol. HbA_{1c} was higher in

Table 1—Characteristics of macrosomic and nonmacrosomic pregnancies in the total population (N = 343)

	No macrosomia (n = 297)			Macrosomia (n = 46)			P
	N	Mean or %	SD	N	Mean or %	SD	
Age of mother (years)	297	33.04	± 5.27	46	34.96	± 4.59	0.02
sAF (AU)	297	1.80	± 0.34	46	2.03	± 0.30	<0.0001
Weeks of amenorrhea at sAF and HbA _{1c} measurement	297	26.91	± 5.80	46	23.67	± 8.35	0.002
SBP (mmHg) (n = 324)	282	115.11	± 13.65	42	114.19	± 12.16	0.68
DBP (mmHg) (n = 324)	282	69.31	± 10.20	42	66.62	± 11.74	0.12
BMI before pregnancy (kg/m ²) (n = 341)	296	26.99	± 7.03	45	27.02	± 5.56	0.98
Family history of diabetes							
No	198	66.67*		36	78.26		0.12
Yes	99	33.33*		10	21.74		
Previous history of macrosomia							
No	276	92.93*		31	67.39		<0.0001
Yes	21	7.07*		15	32.61		
Parity							
0	147	49.49*		13	28.26		0.009
≥ 1	150	50.51*		33	71.74		
Sex of newborn							
Boy	174	58.59*		25	54.35		0.59
Girl	123	41.41*		21	45.65		
Type of diabetes							
Late gestational	191	64.31*		18	39.14		<0.0001
Early gestational	82	27.61*		13	28.16		
Pregestational	24	8.08*		15	32.61		
HbA _{1c} at inclusion (n = 275)							
%	233	5.30	± 0.47	42	5.58	± 0.91	0.004
mmol/mol	233	34.00	± 3.20	42	38.00	± 6.10	
Weeks of gestation at delivery	297	37.06	± 1.72	46	37.07	± 1.73	0.98

P values are univariate logistic regressions. *Percentage value.

Table 2—Association of sAF and potential confounders with macrosomia, assessed by multivariate logistic regression (*n* = 322; 41 with macrosomia vs. 281 without macrosomia)

	OR	95% CI	<i>P</i>
sAF (for 1-AU increase)	4.13	1.46–11.71	0.0075
Weeks of amenorrhea at sAF measurement	0.96	0.90–1.02	0.17
Age of mother	1.06	0.98–1.15	0.15
SBP (mmHg)	1.01	0.97–1.04	0.73
DBP (mmHg)	0.99	0.95–1.02	0.51
BMI before pregnancy	0.98	0.93–1.04	0.51
Type of diabetes			
Late GDM	Reference		0.05
Early GDM	1.21	0.47–3.09	
Pregestational	4.00	1.25–12.80	
Family history of diabetes			
No	Reference		0.047
Yes	0.42	0.18–0.99	
Parity			
0	Reference		0.09
1	1.88	0.76–4.61	
≥2	2.97	1.12–7.85	
Sex of newborn			
Boy	Reference		0.32
Girl	1.45	0.70–3.02	
Weeks of gestation at delivery	1.22	0.95–1.57	0.12

mothers of macrosomic newborns than in other mothers ($5.58 \pm 0.91\%$ or 38 ± 6.1 mmol/mol vs. $5.30 \pm 0.47\%$ or 34 ± 3.2 mmol/mol; $P = 0.004$). The relation between maternal sAF and macrosomia remained significant (OR 3.27 [95% CI 1.03–10.42]) after introducing the HbA_{1c} in the multivariate model (Table 4).

One hundred eighty-three women had a parity ≥ 1 (57%), and 33 of them had a macrosomic newborn. For these women, the relation between maternal sAF and macrosomia remained significant (OR 4.88 [95% CI 1.10–21.67]) after introducing a previous history of macrosomia (OR 3.38 [95% CI 1.16–9.82]) in the multivariate model also adjusted for all of the other covariables (Table 5).

DISCUSSION

In 343 women with hyperglycemia during pregnancy, we found that sAF was 11% higher during pregnancy for mothers who later delivered a macrosomic newborn. The risk of macrosomia associated with sAF remained significant after adjusting for several potential confounding factors, including the type of diabetes (pregestational diabetes and early and late GDM), the family history of diabetes, and parity, which were also related to later macrosomia. The relation between sAF and later macrosomia also remained significant after adjusting for HbA_{1c} when available. In the 303 women with only GDM, sAF was also related to macrosomia, and this shows that this relation was not skewed by the high sAF in women with pregestational diabetes, who are already known to have

Table 3—Association between sAF and macrosomia in the group of women with GDM only (no pregestational diabetes), assessed by multivariate logistic regression (*n* = 289*; 31 with macrosomia vs. 258 without macrosomia)

	OR	95% CI	<i>P</i>
sAF (for 1-AU increase)	3.80	1.20–12.00	0.02
Weeks of amenorrhea at sAF measurement	0.92	0.56–1.00	0.06
Age of mother	1.09	0.99–1.19	0.07
SBP (mmHg)	1.01	0.97–1.04	0.63
DBP (mmHg)	0.99	0.95–1.03	0.49
BMI before pregnancy	1.01	0.94–1.09	0.70
Type of diabetes			
Late GDM	Reference		0.84
Early GDM	0.90	0.32–2.51	
Family history of diabetes			
No	Reference		0.10
Yes	0.46	0.18–1.16	
Parity			
0	Reference		0.21
1	1.91	0.69–5.29	
≥2	2.62	0.88–7.48	
Sex of newborn			
Boy	Reference		0.29
Girl	1.56	0.68–3.56	
Weeks of gestation at delivery	1.27	0.96–1.68	0.09

*Fourteen women with missing data for at least one potential confounder among the 303 women with GDM were not included in the multivariate analysis.

greater risk for large infants: ORs were similar between the group with GDM only and the group with all types of diabetes. Because GDM is usually managed without knowing the previous glycemic status, the prognostic value of sAF in these patients seems an important finding. In the unique previous study of sAF in pregnancy that reported perinatal outcomes, the relation between sAF and LGA babies did not reach significance, probably due to a lower number of participating women (60 patients with GDM) (10).

Fetal macrosomia is a serious problem, associated with numerous perinatal complications (11) and increased risks of obesity, T2D, and arterial hypertension in adulthood (12). The maternal age (13) and parity (14) are well known to be associated with a higher risk of macrosomia. Maternal hyperglycemia, as present in our participants, is a major risk factor for macrosomia, with a continuous relation between glucose levels during pregnancy and birth weights (15).

Despite the favorable effect of glucose control (16), high rates of macrosomia are still reported: 15% for GDM (17) to 40–50% for type 1 diabetes (T1D) (18). Macrosomia was slightly less frequent in our population (11% for GDM and 38% for pregestational diabetes), probably due to overall good glucose control. The very high rates of macrosomia in pregestational diabetes may result from higher but also

Table 4—Association between sAF and macrosomia with further adjustment for HbA_{1c}, assessed by multivariate logistic regression (n = 263*; 38 with macrosomia vs. 225 without macrosomia)

	OR	95% CI	P
sAF (for 1-AU increase)	3.27	1.03–10.42	0.04
Weeks of amenorrhea at sAF measurement	0.96	0.90–1.02	0.21
Age of mother	1.07	0.98–1.18	0.12
SBP (mmHg)	1.01	0.97–1.04	0.73
DBP (mmHg)	1.00	0.96–1.04	0.88
BMI before pregnancy	0.98	0.92–1.04	0.54
Type of diabetes			
Late GDM	Reference		0.08
Early GDM	1.20	0.43–3.37	
Pregestational	4.71	1.17–18.92	
Family history of diabetes			
No	Reference		0.01
Yes	0.28	0.11–0.76	
Parity			
0	Reference		0.22
1	0.61	0.22–1.71	
≥2	1.75	0.63–4.86	
Sex of newborn			
Boy	Reference		0.52
Girl	1.31	0.58–2.99	
Weeks of gestation at delivery	1.18	0.89–1.57	0.24
HbA _{1c} (%)	1.13	0.52–2.49	0.75

*Twelve women with missing data for at least one potential confounder among the 275 women with HbA_{1c} available were not included in the multivariate analysis.

Table 5—Sensitivity analysis by adjusting for macrosomia in a previous pregnancy, only in multiparous women (N = 172*; 30 with macrosomia vs. 142 without macrosomia)

	OR	95% CI	P
sAF (for 1-AU increase)	4.88	1.10–21.67	0.04
Weeks of amenorrhea at sAF measurement	0.94	0.88–1.02	0.13
Age of mother	1.05	0.94–1.16	0.41
SBP (mmHg)	1.02	0.97–1.06	0.47
DBP (mmHg)	0.99	0.94–1.04	0.72
BMI before pregnancy	0.96	0.89–1.04	0.30
Type of diabetes			
Late GDM	Reference		0.24
Early GDM	1.25	0.40–3.91	
Pregestational	3.57	0.80–15.98	
Family history of diabetes			
No	Reference		0.07
Yes	0.37	0.13–1.10	
Parity			
1	Reference		0.63
≥2	1.28	0.47–3.47	
Sex of newborn			
Boy	Reference		0.54
Girl	1.36	0.51–3.64	
Weeks of gestation at delivery	1.20	0.85–1.67	0.30
Previous history of macrosomia			
No	Reference		
Yes	3.38	1.16–9.82	0.02

*Eleven women with missing data for at least one potential confounder among the 183 women with parity ≥1 were not included in the multivariate analysis.

earlier hyperglycemia during pregnancy. Although the third trimester HbA_{1c} best relates to birth weight in pregnant women with T1D (19), relations with HbA_{1c} in the second (18) or even first trimester (20) have been reported. For GDM, early diagnosis before 12 weeks of gestation (21) and early HbA_{1c} ≥5.9% or 41 mmol/mol (22) have been related to higher birth weights. In our study, the risk of later macrosomia was fourfold increased for pregestational diabetes, whereas it was nonsignificantly increased for early GDM compared with late GDM. The relationship between glucose levels in early pregnancy and macrosomia points to the interest of a marker that could reflect previous glucose levels.

sAF reflects the accumulation of AGEs in tissues (5), which is a long-time process: the half-life of skin collagen is ~20 years (23). We have reported that sAF related to diabetes, fasting glycemia, and HbA_{1c} 10 years before in elderly participants from the general population in the three-city cohort (24). In patients with T1D, sAF relates to the HbA_{1c} of the previous years (25). In pregnant hyperglycemic women, sAF is higher in cases of pregestational diabetes (10), with a gradual increase according to indicators of previous hyperglycemia, such as early GDM, and history of GDM or macrosomia in previous pregnancies

(8), as recently confirmed (26). HbA_{1c} only reflects the mean glucose levels of the three previous months, and this relation is altered in pregnancy due to changes in the turnover of hemoglobin and to iron deficiency (27): the HbA_{1c} was not a better predictor of birth weight in the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study, as compared with the glucose levels during oral glucose tolerance tests (15), but it was related to macrosomia in pregestational diabetes (19,28) and GDM (22). The relationship between sAF and macrosomia was, however, still significant after adjusting for HbA_{1c} in our study. This may be due to a better value of sAF as a marker of long-term glucose memory, but it also suggests that the relation between sAF and macrosomia may not only rely on previous hyperglycemia.

High sAF in mothers of macrosomic newborns may relate to a direct effect of AGEs on the prognosis of diabetic pregnancies. In a pioneer work, Mericq et al. (29) found that the concentrations of AGEs in maternal blood correlated with their concentrations in the blood of their newborns and predicted high insulin and low adiponectin levels 1 year later. High levels of serum AGEs have been measured in pregnant diabetic animals, related to fetal development defects (30). High levels of serum AGEs were also reported in human GDM (31), related to adverse

perinatal outcomes such as birth asphyxia, congenital malformations, or stillbirth (32), but not to LGA. AGEs are thought to play a role in preeclampsia (33), and high sAF was reported in former preeclamptic women (34), but they may result from, rather than precede, preeclampsia (35); in our study, blood pressures during pregnancy were not associated with macrosomia. The role of AGEs has also been suspected in neural tube defects (36) and autism (37) that have been related to diabetic pregnancies (38,39).

Some limitations of our study must be kept in mind. The sAF measurement is based on the fluorescent properties of some AGEs, correlated to their concentrations in the skin (5), but it does not directly measure their concentrations. An indirect noninvasive assessment of the accumulation of AGEs in tissues seems, however, an interesting add-on to the measurements of serum concentrations of AGEs. sAF varies with skin pigmentation, and the AGE Reader cannot reliably measure sAF of participants with phototypes 5 and 6 (black and very dark skin in practice); our population was mainly Caucasian. It has recently been reported that ethnic data improve the performance in sAF-based cardiovascular and diabetes risk estimation (40). However, we could not categorize the participants according to their ethnicity because this is not allowed by French law. Macrosomia, defined by the French Haute Autorité de Santé (41) as birth weight $\geq 4,000$ g and/or LGA, is an imperfect criteria. Birth weight does not consider the gestational age, and LGA is based on reference charts that do not take account of factors that may influence fetal growth, such as ethnicity, maternal morphology, and parity. The birth weight, delivery date, or sex of the newborn was sometimes collected by phone call (10% of the total data). Gestational weight gain and HbA_{1c} at the end of pregnancy were not available. The sAF was not measured at the same time of pregnancy for all of the participating women, but we do not think that this could affect the validity of our analyses because de Ranitz-Greven et al. (10), who performed repeated measurements, reported a slight decrease during normal pregnancies but no significant change of sAF in pregnant women with diabetes. Our study does not have a control group composed of pregnant women without hyperglycemia, as this type of patient is not referred to our diabetology department.

In summary, our work shows that sAF, a surrogate marker of AGE accumulation in tissues, is predictive of macrosomia in the offspring of pregnant women with diabetes. sAF has already been shown to predict long-term vascular complications in both T1D (42) and T2D (43) due to its value as a marker of the memory of hyperglycemia, due to the direct deleterious effects of the accumulated AGEs, or both. As its measurement is simple and noninvasive, sAF seems a promising biomarker for the prediction of diabetic complications in pregnancy.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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