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]

Diabetes 2019;68:1663–1669 | https://doi.org/10.2337/db18-0906

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 ≥4,000 g and/or large for gestational age ≥90th 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 ∼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 ≥4,000 g or large for gestational age (LGA) ≥90th 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.

[1]Nutrition-Diabetology, CHU de Bordeaux, Hôpital Haut-Lévêque, Pessac, France
[2]University 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

Received 22 August 2018 and accepted 18 May 2019

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/m^2, 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 ~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 Pédatrie, Obstétrique et Gynécologie. Macrosomia was defined by birth weight ≥4,000 g and/or LGA ≥90th 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 ± 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 ≥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/m^2, 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 ± 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 ≥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 ≥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 ± 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 ($n = 46$)			
	N	Mean or %	SD	*N*	Mean or %	SD	*P*
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	*P*
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

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	*P*
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.

mothers of macrosomic newborns than in other mothers (5.58 ± 0.91% or 38 ± 6.1 mmol/mol vs. 5.30 ± 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 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.

Author Contributions. N.F. is the corresponding author, researched data, and wrote the manuscript. A.C.-G. performed all of the statistical analyses and reviewed the manuscript. K.R., C.G., V.G., and L.B. researched data and reviewed the manuscript. C.D., C.H., T.L., M.H., L.A., and K.M. reviewed the manuscript. V.R. researched data and wrote the manuscript. V.R. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. This study was presented in poster form at the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018.

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2007;30(Suppl. 1):S42–S47

2. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002

3. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. Diabetes 2009;58:453–459

4. Catalano PM, McIntyre HD, Cruickshank JK, et al.; HAPO Study Cooperative Research Group. The Hyperglycemia and Adverse Pregnancy Outcome Study: associations of GDM and obesity with pregnancy outcomes. Diabetes Care 2012;35:780–786

5. Meerwaldt R, Graaff R, Oomen PHN, et al. Simple non-invasive assessment of advanced glycation endproduct accumulation. Diabetologia 2004;47:1324–1330

6. Maynard JD, Rohrscheib M, Way JF, Nguyen CM, Ediger MN. Noninvasive type 2 diabetes screening: superior sensitivity to fasting plasma glucose and A1C. Diabetes Care 2007;30:1120–1124

7. Azar M, Stoner JA, Dao HD, et al. Epidemiology of dysglycemia in pregnant Oklahoma American Indian women. J Clin Endocrinol Metab 2015;100:2996–3003

8. Maury E, Savel J, Grouthier V, et al. Is skin autofluorescence a marker of metabolic memory in pregnant women with diabetes? Diabet Med 2015;32:1575–1579

9. Collège national des gynécologues et obstétriciens français; Société francophone du diabète. Gestational diabetes. J Gynecol Obstet Biol Reprod (Paris) 2010;39(Suppl. 2):S139, S338–S342 [in French]

10. de Ranitz-Greven WL, Kaasenbrood L, Poucki WK, et al. Advanced glycation end products, measured as skin autofluorescence, during normal pregnancy and pregnancy complicated by diabetes mellitus. Diabetes Technol Ther 2012;14:1134–1139

11. Chauhan SP, Rice MM, Grobman WA, et al.; MSCE, for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network. Neonatal morbidity of small- and large-for-gestational-age neonates born at term in uncomplicated pregnancies.Obstet Gynecol 2017;130:511–519

12. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 2005;115:e290–e296

13. Rao J, Fan D, Wu S, et al. Trend and risk factors of low birth weight and macrosomia in south China, 2005-2017: a retrospective observational study. Sci Rep 2018;8:3393

14. Koyanagi A, Zhang J, Dagvadorj A, et al. Macrosomia in 23 developing countries: an analysis of a multicountry, facility-based, cross-sectional survey. Lancet 2013;381:476–483

15. Moses RG, Calvert D. Pregnancy outcomes in women without gestational diabetes mellitus related to the maternal glucose level. Is there a continuum of risk? Diabetes Care 1995;18:1527–1533

16. Landon MB, Spong CY, Thom E, et al.; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units

Network. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339–1348
17. Billionnet C, Mitanchez D, Weill A, et al. Gestational diabetes and adverse perinatal outcomes from 716,152 births in France in 2012. Diabetologia 2017;60: 636–644
18. Ladfors L, Shaat N, Wiberg N, Katasarou A, Berntorp K, Kristensen K. Fetal overgrowth in women with type 1 and type 2 diabetes mellitus. PLoS One 2017;12: e0187917
19. Cyganek K, Skupien J, Katra B, et al. Risk of macrosomia remains glucose-dependent in a cohort of women with pregestational type 1 diabetes and good glycemic control. Endocrine 2017;55:447–455
20. Rey E, Attié C, Bonin A. The effects of first-trimester diabetes control on the incidence of macrosomia. Am J Obstet Gynecol 1999;181:202–206
21. Sweeting AN, Ross GP, Hyett J, et al. Gestational diabetes mellitus in early pregnancy: evidence for poor pregnancy outcomes despite treatment. Diabetes Care 2016;39:75–81
22. Mañé L, Flores-Le Roux JA, Benaiges D, et al. Role of first trimester HbA1c as a predictor of adverse obstetric outcomes in a multi-ethnic cohort. J Clin Endocrinol Metab2017;102:390–397
23. Verzijl N, DeGroot J, Thorpe SR, et al. Effect of collagen turnover on the accumulation of advanced glycation end products. J Biol Chem 2000;275:39027–39031
24. Rajaobelina K, Cougnard-Gregoire A, Delcourt C, Gin H, Barberger-Gateau P, Rigalleau V. Autofluorescence of skin advanced glycation end products: marker of metabolic memory in elderly population. J Gerontol A Biol Sci Med Sci 2015;70: 841–846
25. Genevieve M, Vivot A, Gonzalez C, et al. Skin autofluorescence is associated with past glycaemic control and complications in type 1 diabetes mellitus. Diabetes Metab 2013;39:349–354
26. Cosson E, Gary F, Nguyen MT, et al. Gradual increase in advanced glycation end-products from no diabetes to early and regular gestational diabetes: a case-control study. Diabetes Metab. 2 February 2018 [Epub ahead of print]. DOI: 10.1016/j.diabet.2018.01.007
27. Kurishita M, Nakashima K, Kozu H. Glycated hemoglobin of fractionated erythrocytes, glycated albumin, and plasma fructosamine during pregnancy. Am J Obstet Gynecol 1992;167:1372–1378
28. Glinianaia SV, Tennant PWG, Bilous RW, Rankin J, Bell R. HbA(1c) and birthweight in women with pre-conception type 1 and type 2 diabetes: a population-based cohort study. Diabetologia 2012;55:3193–3203
29. Mericq V, Piccardo C, Cai W, et al. Maternally transmitted and food-derived glycotoxins: a factor preconditioning the young to diabetes? Diabetes Care 2010; 33:2232–2237
30. Tang X, Qin Q, Xie X, He P. Protective effect of sRAGE on fetal development in pregnant rats with gestational diabetes mellitus. Cell Biochem Biophys 2015;71: 549–556
31. Li S, Yang H. Relationship between advanced glycation end products and gestational diabetes mellitus. J Matern Fetal Neonatal Med 2018;21:1–7
32. Guosheng L, Hongmei S, Chuan N, Haiying L, Xiaopeng Z, Xianqiong L. The relationship of serum AGE levels in diabetic mothers with adverse fetal outcome. J Perinatol 2009;29:483–488
33. Chekir C, Nakatsuka M, Noguchi S, et al. Accumulation of advanced glycation end products in women with preeclampsia: possible involvement of placental oxidative and nitrative stress. Placenta 2006;27:225–233
34. Coffeng SM, Blaauw J, Souwer ETD, et al. Skin autofluorescence as marker of tissue advanced glycation end-products accumulation in formerly preeclamptic women. Hypertens Pregnancy 2011;30:231–242
35. Foussard N, Cougnard-Gregoire A, Rajaobelina K, et al. Comment on Kelly et al. Subclinical first trimester renal abnormalities are associated with pre-eclampsia in normoalbuminuric women with type 1 diabetes. Diabetes Care 2018; 41:120-127 (Letter). Diabetes Care 2018;41:e101
36. Li R, Yang P, Chen X, Wang L. Maternal serum AGEs levels in pregnancies associated with neural tube defects. Int J Dev Neurosci 2014;33:57–61
37. Barua M, Jenkins EC, Chen W, Kuizon S, Pullarkat RK, Junaid MA. Glyoxalase I polymorphism rs2736654 causing the Ala111Glu substitution modulates enzyme activity–implications for autism. Autism Res 2011;4:262–270
38. Sukanya S, Bay BH, Tay SS, Dheen ST. Frontiers in research on maternal diabetes-induced neural tube defects: past, present and future. World J Diabetes 2012;3:196–200
39. Xiang AH, Wang X, Martinez MP, et al. Association of maternal diabetes with autism in offspring. JAMA 2015;313:1425–1434
40. Ahmad MS, Kimhofer T, Ahmad S, et al. Ethnicity and skin autofluorescence-based risk-engines for cardiovascular disease and diabetes mellitus. PLoS One 2017;12:e0185175
41. Haute Autorité de Santé. Indications de la césarienne programmée à terme, Méthode recommandations pour la pratique clinique, argumentaire scientifique [Internet], 2012. Available from https://www.has-sante.fr/portail/upload/docs/application/pdf/2012-03/indications_cesarienne_programme_-_argumentaire.pdf. Accessed 9 January 2019
42. Vélayoudom-Céphise F-L, Rajaobelina K, Helmer C, et al. Skin autofluorescence predicts cardio-renal outcome in type 1 diabetes: a longitudinal study. Cardiovasc Diabetol 2016;15:127
43. Gerrits EG, Lutgers HL, Kleefstra N, et al. Skin autofluorescence: a tool to identify type 2 diabetic patients at risk for developing microvascular complications. Diabetes Care 2008;31:517–521