University of Groningen

Skin autofluorescence, a non-invasive biomarker for advanced glycation end products, is not related to the number of pregnancies

van Waateringe, Robert; Truyens, Laura; van den Berg, Paul; Lutgers, Helen L.; Wolffenbuttel, B.H.

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

RESEARCH LETTER

Skin autofluorescence, a non-invasive biomarker for advanced glycation end products, is not related to the number of pregnancies

Highlights
- Skin autofluorescence (SAF) assesses subcutaneous accumulation of advanced glycation end products and has been shown to predict future cardiovascular disease and diabetes.
- A higher number of pregnancies was significantly associated with higher SAF, even after correction for relevant confounders like waist circumference, creatinine clearance, and diabetes status, but not after correction for age.
- Women with the highest SAF *Z*-score had a more unfavorable risk factor profile, with higher body mass index and waist circumference, higher blood pressure, lower high-density lipoprotein cholesterol, and higher triglyceride levels.

Robert P. VAN WAATERINGE,[1] Laura TRUYENS,[2] Paul P. VAN DEN BERG,[3] Helen L. LUTGERS[4] and Bruce H.R. WOLFFENBUTTEL [1]

[1]Department of Endocrinology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, [2]University of Louvain, Louvain, Belgium, [3]Department of Gynecology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands, and [4]Department of Internal Medicine, Medisch Centrum Leeuwarden, Leeuwarden, The Netherlands

To the Editor

The role of advanced glycation end products (AGEs) in the pathophysiology of diabetes-related complications and aging has been studied extensively. The AGEs represent chronic exposure to hyperglycemia and oxidative stress. Tissue AGE accumulation can be assessed non-invasively by measuring skin autofluorescence (SAF) with a so-called AGE reader. Markers of oxidative stress are elevated during pregnancy, which can, in turn, increase the formation of AGEs.[1] One study reported that SAF levels were higher in pregnant women with pre-existing diabetes than in women with gestational diabetes and women without diabetes.[2]

Preliminary data from our group suggested that SAF increases during pregnancy and does not return to pre-pregnancy levels (B. Groen et al., unpublished data, 2014). This phenomenon may be caused by increased oxidative and glycemic stress during pregnancy. Therefore, the aim of the present study was to assess the relationship between SAF and the number of pregnancies.

Methods

Subjects included in the study were participants from the Lifelines Cohort Study, a large population-based cohort study in the northern region of the Netherlands (www.lifelines.net, accessed 24 December 2017). The Lifelines study was approved by the Medical Ethics Committee of the University Medical Center Groningen. Written informed consent was obtained from all participants. The present study included women of Western European descent aged between 18 and 80 years for whom an SAF measurement was available. Subjects with type 1 and type 2 diabetes were excluded, as were as those with missing data for diabetes, leaving 47 834 individuals for analysis. Subjects completed a questionnaire on medical history, past and current diseases, use of medication, and health behavior. The questionnaire also included information on previous pregnancies and childbirth. Women were asked how many times they had been pregnant and how many children were born. In the present study, SAF was calculated as the mean of three consecutive measurements using an AGE Reader (DiagnOptics

Technologies, Groningen, Netherlands).[3] Age-adjusted SAF (*Z*-scores) was calculated because SAF is strongly affected by aging.[3]

Data are given as the mean $\pm$SD or as the median with interquartile range (IQR) in the case of non-normally distributed data. Linear regression analysis was performed to examine the association between the number of pregnancies and SAF. In the multivariate models, we adjusted for relevant factors, such as waist circumference, body mass index (BMI), renal function, and smoking. Two-tailed $P < 0.001$ was considered significant.

Results

The clinical characteristics of the study population are given in Table S1, available as Supplementary Material to this paper. Mean subject age was 44 $\pm$12 years, mean waist circumference was 87 $\pm$12 cm, and mean BMI was 25.8 $\pm$4.6 kg/m^2. The median number of pregnancies was 2.0 (IQR 1.0–3.0). In total, 20.5% of women had not been pregnant, 42% reported one to two pregnancies, 30% reported three to four pregnancies, and 7.5% reported five or more pregnancies. A higher number of pregnancies was associated with higher SAF, which persisted after correction for waist circumference and renal function ($P < 0.0001$). However, after further correction for age, SAF was no longer associated with the number of pregnancies ($P = 0.713$; Table 1). Fig. 1 shows that SAF *Z*-scores are comparable in the various groups of women divided according to the number of pregnancies. Women in the highest quartile of the SAF *Z*-score had a higher prevalence of metabolic syndrome, as well as higher BMI, waist circumference, glucose, HbA1c, and lipids (all
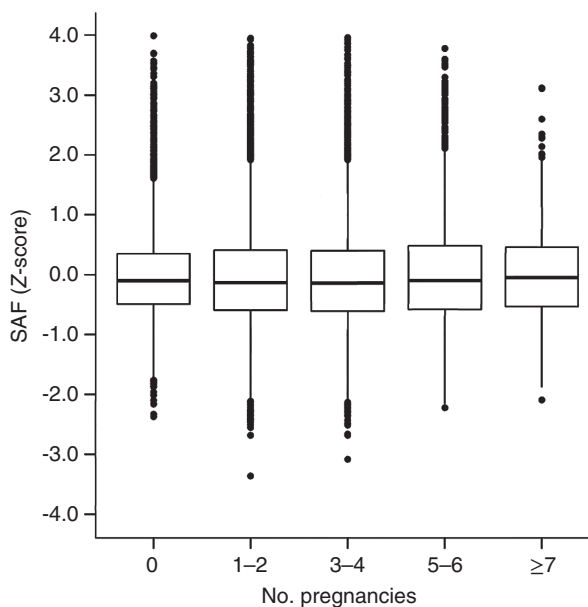

Figure 1 Number of pregnancies and age-corrected skin autofluorescence (SAF) Z-score. The boxes show the interquartile range, with the median value indicated by the horizontal line; whiskers show the range. Dots indicate outliers.

$P < 0.01$) than women in the other three quartiles, and a similar number of pregnancies compared with those in the lowest quartile (Table S2).

Discussion

After correction for important confounders, SAF increased with the number of pregnancies in women from the general population. However, after correction for age, this association was no longer significant. The increased oxidative stress that occurs during pregnancy may significantly affect SAF measurements. Indeed, it has been reported that SAF is elevated in women with pre-eclampsia and associated with increased carotid artery intima–media thickness, a marker for atherosclerosis.[4] Moreover, SAF was associated with higher blood pressure, triglycerides, and C-reactive protein levels, indicating the potential cardiovascular risk associated with these factors.[5] Therefore, we postulate that the effect of pregnancy on SAF may only be restricted to pathological pregnancies, such as those complicated by pre-eclampsia.[4,5] Unfortunately, the Lifelines dataset did not record any complications of pregnancy.

Two important studies have reported on the association between reproductive history and cardiovascular health. One of these studies reported that a higher number of pregnancies was associated with lower cardiovascular mortality,[6] whereas the other study showed that the

Table 1 Univariate and multivariate analyses for skin autofluorescence

Model	Parameters	β	*P*-value	R^2 (%)
1	No. pregnancies	0.061	<0.0001	5.3
2	No. pregnancies	0.0003	0.800	30.7
	Age	0.020	<0.0001	
3	No. pregnancies	0.0031	<0.0001	19.7
	Waist	0.013	<0.0001	
	GFR	−0.006	<0.0001	
4	No. pregnancies	0.030	<0.0001	20.5
	Waist	0.012	<0.0001	
	GFR	−0.006	<0.0001	
	Diabetes or glucose	0.084	<0.0001	
5	No. pregnancies	−0.0001	0.941	31.3
	Age	0.17	<0.0001	
	Waist	0.004	<0.0001	
	GFR	−0.001	<0.0001	
	Diabetes	0.015	<0.0001	

GFR, glomerular filtration rate.

number of pregnancies or live births was associated with higher left ventricular mass and end-systolic volume.[7] A recent review suggested that pre-eclampsia is an under-recognized risk factor for ischemic heart disease, chronic hypertension, peripheral vascular disease, and stroke.[8]

In conclusion, in the present study SAF increased with a higher number of pregnancies, but not after correction for participants' age. Those with the highest age-corrected SAF had a worse risk factor profile for future cardiovascular disease.

Acknowledgements

Disclosure

None declared.

References

1. Toescu V, Nuttall SL, Martin U, Kendall MJ, Dunne F. Oxidative stress and normal pregnancy. *Clin Endocrinol (Oxf)*. 2002; **57**: 609–13.
2. De Ranitz-Greven WL, Kaasenbrood L, Poucki WK et al. Advanced glycation end products, measured as skin autofluorescence, during normal pregnancy and preg-nancy complicated by diabetes mellitus. *Diabetes Technol Ther*. 2012; **14**: 1134–9.
3. Meerwaldt R, Graaff R, Oomen PHN et al. Simple non-invasive assessment of advanced glycation endproduct accumulation. *Diabetologia*. 2004; **47**: 1324–30.
4. Blaauw J, Smit AJ, van Pampus MG et al. Skin auto-fluorescence, a marker of advanced glycation end prod-ucts and oxidative stress, is increased in recently preeclamptic women. *Am J Obstet Gynecol*. 2006; **195**: 717–22.
5. Coffeng SM, Blaauw J, Souwer ET et al. Skin autofluor-escence as marker of tissue advanced glycation end-products accumulation in formerly preeclamptic women. *Hypertens Pregnancy*. 2011; **30**: 231–42.
6. Jacobs MB, Kritz-Silverstein D, Wingard DL, Barrett-Connor E. The association of reproductive history with all-cause and cardiovascular mortality in older women: The Rancho Bernardo Study. *Fertil Steril*. 2012; **97**: 118–24.
7. Parikh NI, Lloyd-Jones DM, Ning H et al. Association of number of live births with left ventricular structure and function. The Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J*. 2012; **163**: 470–6.
8. Ahmed R, Dunford J, Mehran R, Robson S, Kunadian V. Pre-eclampsia and future cardiovascular risk among women a review. *J Am Coll Cardiol*. 2014; **63**: 1815–22.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Baseline characteristics of the participating women.
Table S2. Skin autofluorescence *Z*-scores and cardiovascu-lar risk factors.

901

Journal of Diabetes published by John Wiley & Sons Australia, Ltd and Ruijin Hospital, Shanghai Jiaotong University School of Medicine.