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Increased breath markers of oxidative stress in normal pregnancy and in preeclampsia

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KEY WORDS
Preeclampsia
Oxidative stress
Breath
Alkanes
Methylated alkanes

Objectives: The purpose of this study was to compare the intensity of oxidative stress in normal pregnancy, preeclampsia, and nonpregnant women using a breath test.
Study design: We studied primiparous women in third trimester pregnancy (38 uncomplicated, 26 with preeclampsia) and 60 nonpregnant control subjects. Volatile organic compounds (VOCs) in alveolar breath were analyzed by gas chromatography/mass spectroscopy to construct the breath methylated alkane contour (BMAC), a 3-dimensional display of abundance of C4-C20 alkanes and monomethylated alkanes.
Results: The mean volume under curve (VUC) of the BMAC was significantly higher in preeclampsia patients than in normal pregnant women ($P < .003$) and nonpregnant control subjects ($P < .005$). A predictive model employing 5 VOCs distinguished preeclampsia from uncomplicated pregnancy (sensitivity = 92.3%, specificity = 89.7%; cross-validated sensitivity = 88.5%, specificity = 79.3%).
Conclusion: A breath test significantly demonstrated greater oxidative stress in women with preeclampsia than in uncomplicated pregnancy and nonpregnant control subjects. The breath test accurately identified women with established preeclampsia, but further studies are required to determine if this test can predict the onset of disease.

Preeclampsia is a complication of pregnancy characterized by hypertension, edema, and proteinuria, and no single test or combination of tests has yet been shown to predict its onset with accuracy.[1] A number of risk factors for preeclampsia have been identified, including increased plasma cellular fibronectin concentrations,[2] history of preeclampsia, elevated screening mean arterial pressure, and low unconjugated estriol concentration.[3] However, in clinical practice, preeclampsia is defined by its clinical manifestations, and is often discovered late in its course. An objective screening test to predict the onset of preeclampsia would be clinically valuable in order to identify women who require closer clinical monitoring during pregnancy, and also to aid in evaluating new preventive therapies before the onset of clinical symptoms or signs.[4]

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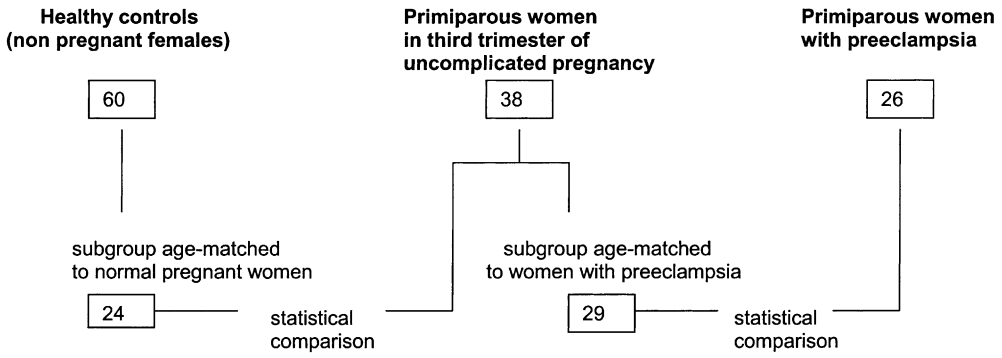

Figure 1 Plan of data analysis. Breath tests for the BMAC were performed in three groups of women: healthy control subjects (nonpregnant females), primiparous women in their third trimester of pregnancy, and primiparous women with preeclampsia. The BMAC is affected by age, so that statistical comparisons of the BMAC between groups were performed in age-matched subgroups that had been selected as shown in this figure.

Because increased oxidative stress has been implicated in the etiology of preeclampsia,[5] a marker of oxidative stress could potentially provide such a screening test. Oxidative stress originates in the mitochondria as a byproduct of oxidative metabolism. When oxygen accepts electrons, the main products are water and energy, but a number of other products known collectively as reactive oxygen species (ROS) are also formed. ROS are highly toxic; they leak into the cytoplasm and inflict a constant barrage of oxidative damage to DNA, proteins, lipids, and other biologically important molecules.[6] This process generates a variety of metabolic products, including oxidized thiols,[7] lipid peroxides,[8] and isoprostane,[9] which have been employed as biomarkers of increased oxidative stress in preeclampsia.

Oxidative stress can also be estimated with breath testing because lipid peroxidation of polyunsaturated fatty acids in membranes generates alkanes such as ethane and pentane, which are excreted in the breath as volatile organic compounds (VOCs).[10] Breath tests for these VOCs have demonstrated increased oxidative stress in breast cancer,[11] rheumatoid arthritis,[12] heart transplant rejection,[13] acute myocardial infarction,[14] schizophrenia,[15] and bronchial asthma.[16]

However, a biomarker of oxidative stress such as breath pentane is an inherently nonspecific marker of disease because it is increased in a wide variety of conditions. We have reported a new index of oxidative stress, the breath methylated alkane contour (BMAC), comprising a 3-dimensional surface plot of the abundance in breath of C4 to C20 alkanes and their monomethylated derivatives.[17] The BMAC incorporates 107 different VOCs, and their pattern is altered in a distinctive fashion in different conditions, including lung cancer,[18] breast cancer,[19] unstable angina,[20] oxygen breathing,[21] and aging.[22] In this study, we employed the BMAC to compare the intensity of oxidative stress in 3 groups of women: normal third trimester pregnancy, women with preeclampsia, and nonpregnant control subjects.

Material and methods

Human subjects

The design of the study is shown in Figure 1. The research was approved by the institutional review board of the Sisters of Charity Health Care System, St Vincent's Campus, Staten Island, New York, and all women gave their signed informed consent to participate. All subjects in this study were nonsmokers. This was a cross-sectional study of 3 groups of women:

Uncomplicated pregnancy (n = 38)

All subjects were singleton primigravidas selected from the general obstetric population with gestational age $\geq$26 weeks, no chronic medical disorders, and not in labor. They were normotensive and nonobese. Patients with a history of renal disease, diabetes, or significant perinatal complications were excluded.

Preeclampsia (n = 26)

All subjects were primigravida with gestational age>26 weeks and no chronic medical disorders (apart from two subjects with gestational diabetes mellitus) and not in labor. Preeclampsia was defined as blood pressure>140/90 mm Hg on 2 separate occasions 4 to 6 hours apart with concordant proteinuria. Proteinuria was defined as a urinary dipstick value>1+ (30mg/dL), or a 24-hour urine collection with a protein excretion of>300 mg. Patients taking aspirin, antihypertensive medication, or antioxidants (other than traditional prenatal vitamins) were excluded, as were those with obesity, history of chronic hypertension, insulin-dependent diabetes, or renal disease. Only those patients with

Table I Characteristics of the normal pregnant women and patients with preeclampsia

Characteristics	Normal pregnancy (n = 38)	Preeclampsia (n = 26)
Maternal age (y)	24.8 (4.7)	28.1 (6.2)
Gestational age (wks)	33.5 (4.0)	35.5 (4.67)
Blood pressure (mm Hg)		
Systolic	110 (7)	160.7 (19.4)
Diastolic	63 (8)	94.6 (5.3)
Maternal weight (lb)	158 (29.3)	178 (42.5)
Proteinuria (mg/24h)	—	2246 (566)
Urine dipstick > 1+ (No.)	—	26
Race (No.)		
White	22	17
Hispanic	3	3
African American	13	6
Asian	0	0
Gestational age at delivery (wks)	39.2 (1.2)	36.3 (4.67)
Birth weight (g)	3407 (220)	2361.3 (1085)
NICU admissions	1	7
5 min Apgar <7	0	4

Values are mean and (SD)
NICU, Neonatal intensive care unit.

Table II Laboratory investigations in patients with preeclampsia

Serum creatinine (mg/dL)	0.7 (0.9)
Uric acid (mg/dL)	5.7 (5.8)
Platelet count (thous/mcL)	158,000 (27)
AST (u/L)	35.7 (26)
ALT (u/L)	34.9 (19)
LDH (uU/L)	197.7 (48.3)
Total bilirubin (mg/dL)	0.5 (0.14)
Direct bilirubin (mg/dL)	0.2 (0.35)
Fibrinogen (mg/dL)	413.8 (71.8)
Prothrombin time (ratio)	12.3 (1.9)
Partial thromboplastin time (sec)	27.8 (2.3)
WBC	10.86 (2.74)
Hemoglobin (g/dL)	12.08 (1.02)
Hematocrit (%)	34.8 (3.2)

Values are mean and (SD)
AST, Aspartate amino transferase; *ALT*, alanine aminotransferase; *LDH*, lactate dehydrogenase; *WBC*, White blood cell count.

proteinuric hypertension classified as mild preeclampsia by the American College of Obstetrics and Gynecology Criteria were included.[23]

Healthy controls (n = 60)

The healthy nonpregnant control subjects were recruited from employees of the medical center. All were nonpregnant females aged 17 to 40 years, with no chronic medical disorders. None of the women had delivered a baby or conceived during the year before the breath test. Clinically obese women, and those women taking hormonal contraception were excluded.

Location and time of breath tests

Breath collections were performed in the labor and delivery unit by a research assistant (AA). In the preeclampsia group, breath samples were collected when the patient presented for evaluation, and before initiation of MgSo4 or antihypertensives. Samples were collected from the other patients between 8 a.m. and 4 p.m. daily, at least 2 hours after meals.

Breath collection and assay

This method has been previously described.[24,25] In summary, a portable breath collection apparatus was employed to capture the VOCs in 1.0 l breath and in 1.0 l room air onto separate sorbent traps. Each subject wore a nose clip while breathing in and out of the disposable mouthpiece of the apparatus for 2.0 minutes. Breath samples could be collected without discomfort because light flap valves in the mouthpiece presented low resistance to respiration. VOCs captured in sorbent traps were analyzed by automated thermal desorption, gas chromatography, and mass spectroscopy.

Derivation of BMACs

This method has been previously described.[17] Data from the assays of breath and air VOCs were employed to generate 3-dimensional surface plots of C4 to C20 n-alkanes and their monomethylated derivatives. For each breath VOC, V_b denotes the area under the curve associated with the chromatogram peak, and I_b denotes the analogous area associated with the internal standard used to normalize the data (0.25 mL 2 ppm 1-bromo-4-fluoro-benzene; Supelco, Bellefonte, Pa). V_a and I_a denote corresponding areas derived from the associated sample of room air. The alveolar gradient[25] of each VOC was then determined as:

$$\text{alveolar gradient} = V_b/I_b - V_a/I_a.$$

The mean alveolar gradients of these VOCs were computed for each group of subjects and displayed in surface plots showing the carbon chain length on the x-axis, the methylation site on the z-axis, and the mean alveolar gradient on the y-axis.

Analysis of data

The volume under curve (VUC) of each BMAC was determined, and VUC values in the 3 groups were compared. Forward step-wise discriminant analysis[26] was used to identify the combination of VOCs that provided the best discrimination between women with preeclamp-

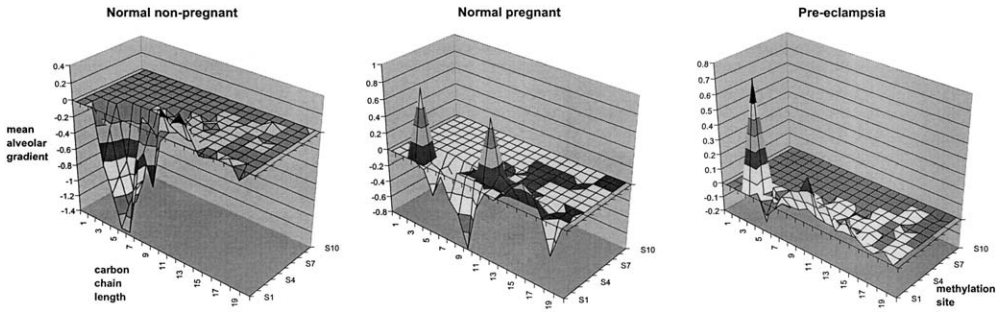

Figure 2 BMACs in 3 groups of women. The BMAC is a display of the abundance (alveolar gradients) of C4 to C20 alkanes and monomethylated alkanes in breath. The alveolar gradient (y-axis) is the concentration in breath minus the concentration in room air, and varies with the rate of synthesis minus the rate of clearance. The x-axis displays the chain length of straight chain n-alkanes methylated at one site, and the z-axis displays the methylation site. This figure includes n-alkanes, showing them as methylated at C1. For example, an alkane with carbon chain length = 4 (butane) becomes the C5 alkane pentane when methylated at C1. BMACs are shown for the healthy control subjects (nonpregnant females), primiparous women in their third trimester of pregnancy, and primiparous women with preeclampsia. The mean value for each of the age-matched subgroups selected in Figure 1 is shown. It is apparent that peaks are predominantly negative in the nonpregnant females and predominantly positive in preeclampsia group, and intermediate in the normal pregnant women.

sia and primiparous women in the third trimester of uncomplicated pregnancy, in order to construct a predictive model. The accuracy of this predictive model was first tested by cross-validation using a leave-one-out technique, in which each subject was classified using an equation derived from all other subjects.[27] A receiver operating characteristic (ROC) curve[28] was constructed to display the sensitivity and specificity of the breath test.

Results

Human subjects

Table I shows demographic and clinical data for the preeclampsia and normal pregnancy groups. No significant perinatal complications developed in the normal pregnancy group. Table II shows the laboratory data in the preeclampsia group. No cases of HELLP Syndrome, eclampsia, or abruption developed. There were no maternal or neonatal deaths. All patients in the preeclampsia group received MgSo4 before delivery and for 24 hours postpartum.

Breath test

Mean BMACs in the 3 groups are shown in Figure 2. The mean VUCs of the BMACs are shown in Figure 3. Because the data did not meet the requirements for parametric testing (namely homoskedasticity and normal distribution), the nonparametric Kruskal-Wallis test was used. The overall P value for the hypothesis that all 3 medians were equal was $P < .002$. This was followed by pair-wise comparisons using a Bonferroni adjustment for multiple tests. The significance cutoff point was set at $P = .025$. Differences were significant between nonpregnant control subjects vs preeclampsia patients ($P < .005$), and normal pregnant women vs preeclampsia patients ($P < .003$) (Figure 3). Discriminant analysis identified 5 VOCs in the BMAC as the optimal discriminators of preeclampsia (Table III). A predictive

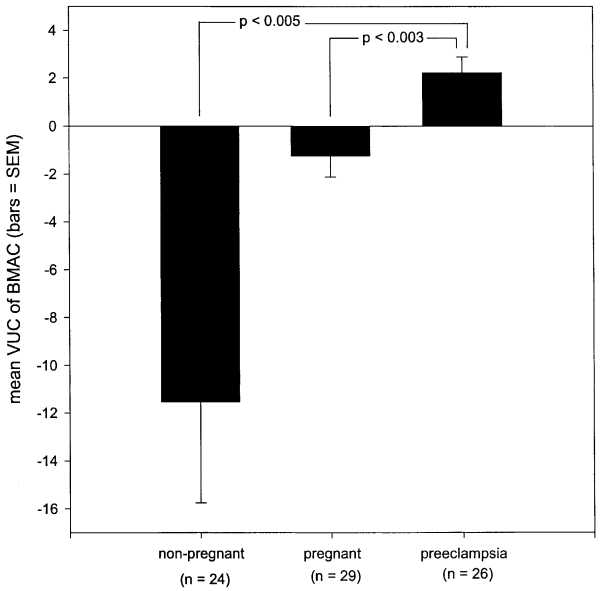

Figure 3 Volume under the curve (VUC) of the BMACs in 3 groups of women. The BMAC incorporates 107 different VOCs, but can be reduced to a single value, the VUC. This figure displays the VUCs (with SEM) of the BMACs displayed in Figure 2. This figure demonstrates that the apparent differences between the BMACs in Figure 2 are statistically significant.

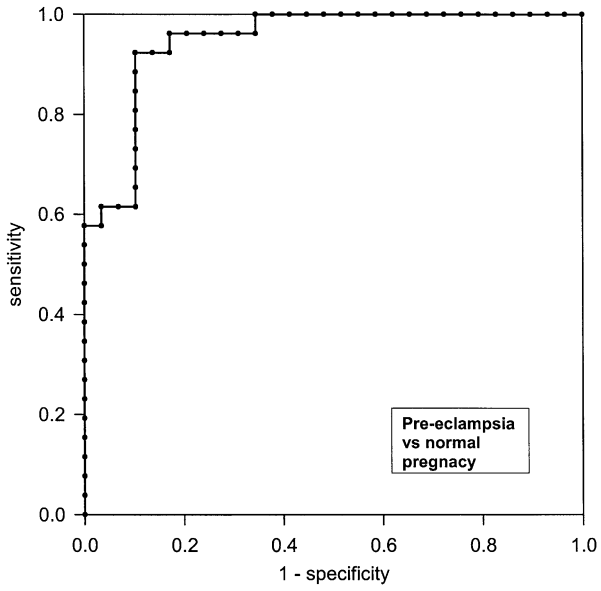

Figure 4 Receiver operating characteristic (ROC) curve—preeclampsia vs normal pregnancy. The probability of preeclampsia was determined in 2 groups of women (normal pregnancy and preeclampsia) using a predictive model derived from the differences between their BMACs. The ROC curve demonstrates the continuum of sensitivity and specificity encountered as the cutoff point (predicted probability of disease) was varied. The optimal combination (observed at the "shoulder" of the curve at top left) was sensitivity = 92.3% and specificity = 89.7% (cross-validated sensitivity = 88.5 and specificity = 79.3%). This ROC curve describes the performance of the breath test in women with established disease, and additional studies need to be performed at earlier stages of pregnancy to determine if the breath test can predict the onset of preeclampsia.

model employing these VOCs identified women with preeclampsia with sensitivity = 92.3% and specificity = 89.7% (cross-validated sensitivity = 88.5% and specificity = 79.3%). The ROC curve is shown in Figure 4.

Comment

The abundance of breath markers of oxidative stress was significantly higher in preeclampsia than in the third trimester of uncomplicated pregnancy or in nonpregnant control subjects. A predictive model employing 5 VOCs in the BMAC was sensitive and specific for preeclampsia. Although the pathogenesis of preeclampsia remains poorly understood, these findings are consistent with previous reports that oxidative stress plays an important role.[29-32] Various mechanisms for the increase in oxidative stress have been proposed, including the promotion of free radical reactions by "cross-talk" between the diseased placenta and maternal dyslipidemia.[5]

Table III Breath test discriminators between preeclampsia and normal pregnancy

Undecane
6-methyltridecane
2-methylpentane
5-methyltetradecane
2-methylnonane

Discriminant analysis of the BMACs (shown in Fig 2) identified these 5 components of the BMAC as optimal discriminators between uncomplicated pregnancy and preeclampsia ($P < 10^{-4}$ for each VOC). These VOCs were incorporated into a predictive model that accurately discriminated between the 2 groups. The sensitivity and specificity of this model are shown in Fig 4.

Several studies have employed different markers to estimate oxidative stress, and there is agreement that the level of lipid peroxides in blood is generally higher in pregnant women than in nonpregnant women.[33] However, comparisons between normal pregnancy and preeclampsia have yielded conflicting results with different markers. Studies employing plasma F(2)-isoprostanes[34] and the ratios of free-to-oxidized cysteine, homocysteine, and cysteinylglycine[7] found significant increases in preeclampsia.compared with normal pregnancy. However, studies employing lipid hydroperoxides, malondialdehyde,[35] and breath ethene[36] found no difference between the 2 groups. The central difficulty in interpreting these apparent disparities is that there are no studies comparing the sensitivity and specificity of the different markers of oxidative stress. One possible explanation is that markers such as the BMAC and F(2)-isoprostanes are more sensitive to increased oxidative stress in preeclampsia than lipid hydroperoxides and breath ethene. In support of the sensitivity of the BMAC, it has demonstrated significant increases in oxidative stress in normal breathing oxygen[21] and in aging,[22] and has provided a sensitive and specific marker of lung cancer,[18] breast cancer,[19] heart transplant rejection,[37] and unstable angina.[20] The strength of the BMAC, compared with most other markers, is that it comprises the aggregate of 107 different end products of oxidative stress.

The physiologic role of oxidative stress during normal pregnancy is poorly understood; it may result from the maternal response to pregnancy when spiral arteries are transformed into low resistance vessels around the invading trophoblast.[38] However, increased oxidative stress may also originate in the fetus because ROS act as signal transducers during normal growth and development. ROS are essential regulators of cell proliferation and differentiation; eg, in the central and peripheral nervous system, ROS initiate the establishment of neuronal patterns and promote subsequent neurogenesis.[39] The process may be mediated by growth factor or cytokine stimulation, which causes a rapid increase in intracellular ROS.[40]

This was a cross-sectional study performed in women with established preeclampsia. Consequently, the clinical value of this breath test as a predictor of preeclampsia is unknown because it is not known whether increased oxidative stress precedes the onset of disease.[41] Future longitudinal studies are required to determine if increased breath markers of oxidative stress during earlier stages of pregnancy can predict the onset of preeclampsia. In addition, it would be of great interest to determine if increased oxidative stress in preeclampsia and normal pregnancy resolves after delivery.

We conclude that a breath test for oxidative stress accurately identified women with established preeclampsia. Further studies are required to determine if a breath test for oxidative stress performed earlier in pregnancy can identify women at increased risk of developing preeclampsia.

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