RESEARCH LETTER

Plasma Concentrations of Asymmetric Dimethylarginine (ADMA) in Colombian Women With Pre-eclampsia

To the Editor: Worldwide, pre-eclampsia is a leading cause of maternal death, affecting 3% to 5% of all pregnancies.[1] Recently, elevated plasma concentrations of the endogenous nitric oxide synthase inhibitor asymmetric dimethylarginine (ADMA) have been linked to pre-eclampsia and impaired endothelial function.[2-5]

Methods. To assess plasma ADMA concentration in pregnant women living in a high-risk area for pre-eclampsia, we sequentially enrolled, from November 2000 until February 2002, 160 women (67 women with pre-eclampsia [49 moderate and 19 severe cases] and 93 healthy pregnant controls) (TABLE 1) presenting in 4 Colombian study centers in a case-control study. All women were primigravid and younger than 25 years. Inclusion criteria for the pre-eclampsia group were: more than 20 weeks of gestation, blood pressure of 140/90 mm Hg or higher in 2 separate measurements, and proteinuria (≥0.3 g in 24 hours or a urine dipstick reading of ≥2+ for protein with no evidence for urinary tract infection). Controls were clinically healthy women with onset of labor at 37 or more weeks of gestation. None of the controls had hypertension or proteinuria at the onset of labor. Ethnicity (as determined by a validated questionnaire[6]) and exclusion criteria for both groups (history of renal, cardiac, metabolic [diabetic], or autoimmune disease) were assessed by the enrolling physicians. The study was approved by the ethics committee of the Universidad Autónoma de Bucaramanga, Colombia, and all women enrolled provided written informed consent. Plasma concentrations of ADMA, symmetric dimethylarginine, and L-arginine were measured blinded (within-assay and between-assay variations for ADMA, 1.7% and 2.5%, respectively; limit of detection, 0.004 µmol/L) by minor modifications of an established method.[4] Our sample size had a greater than 93% power to detect a 40% difference in plasma ADMA concentrations, with $P<.05$ (2-sided) used to determine statistical significance.

Results. We found no significant differences in plasma ADMA concentrations among Colombian women with pre-eclampsia (TABLE 2). Median (interquartile range) ADMA concentrations in the subgroup of white women (n=12) with pre-eclampsia were not different from those of the rest of the case group (n=55) (0.44 [0.28-0.55] µmol/L vs 0.43 [0.32-0.61] µmol/L; $P=.83$; 95% confidence interval for difference between the medians, –0.15 to 0.13). Within the subgroup of white women ADMA concentrations of pre-eclamptic women (n=12) and healthy pregnant women (n=19) were also not different (0.44 [0.28-0.55] µmol/L vs 0.39 [0.27-0.49] µmol/L; $P=.59$; 95% confidence interval for difference between the medians, –0.11 to 0.18).

Comment. Several possible explanations could be considered for this unexpected finding. It is unlikely that the study was underpowered, as it included the largest number of cases reported to our knowledge. Timing of blood sampling (third tri-

Table 1. Patient Characteristics

Characteristic	Cases (n = 67)	Controls (n = 93)	*P* Value
Maternal age, mean (SD), y*	20.1 (5.4)	19.6 (3.7)	.99
Ethnicity, No. (%)†			
White	12 (17.9)	19 (20.4)	.73
African	8 (11.9)	8 (8.6)	
Indigenous	3 (4.5)	2 (2.2)	
Multiethnic	44 (65.7)	64 (68.8)	
Blood pressure, mean (SD), mm Hg*			
Systolic	152 (16)	118 (14)	<.001
Diastolic	100 (10)	73 (8)	<.001
Gestational age at delivery, median (IQR), wk‡	36.0 (33.8-38.8)	39.0 (38.1-40.3)	<.001
Newborn weight, mean (SD), g*	2455 (784)	3213 (434)	<.001

Abbreviation: IQR, interquartile range.
*By unpaired *t* test.
†By 2-sided Pearson/Monte Carlo test.
‡By 2-sided Mann-Whitney *U* test. Gestational age at delivery corresponds to time point of blood sampling.

Table 2. Plasma Concentrations of ADMA, L-Arginine, and SDMA

	Median (Interquartile Range), µmol/L			
	Cases (n = 67)	Controls (n = 93)	Estimated Difference Between Group Medians (95% CI)	*P* Value*
ADMA concentration	0.43 (0.31-0.56)	0.42 (0.29-0.55)	–0.03 (–0.09 to 0.04)	.42
Pre-eclampsia†				
Moderate (n = 48)‡	0.41 (0.31-0.54)	NA	NA	
Severe (n = 19)‡	0.52 (0.27-0.74)	NA	NA	
L-Arginine concentration	43.0 (18.9-58.9)	29.4 (18.1-56.6)	–3.30 (–11.1 to 4.1)	.39
L-Arginine/ADMA ratio	88.9 (41.8-137.8)	91.4 (37.7-152.2)	3.92 (–17.6 to 25.7)	.92
SDMA concentration§	0.40 (0.31-0.63)	0.37 (0.27-0.52)	–0.07 (–0.16 to 0.02)	.13

Abbreviations: ADMA, asymmetric dimethylarginine; CI, confidence interval; NA, not applicable; SDMA, symmetric dimethylarginine.
*By 2-sided Mann-Whitney *U* test.
†$P = .56$ by Kruskal-Wallis test for healthy pregnant women vs those with moderate pre-eclampsia vs those with severe pre-eclampsia.
‡Moderate pre-eclampsia defined as blood pressure ≥140/90 mm Hg, proteinuria (≥0.3 g/24 hours [or ≥2+ urine dipstick] and <5 g/24 hours [or <4+ urine dipstick], and platelet count ≥100 000 cells/µL. Severe pre-eclampsia defined as blood pressure ≥160/110 mm Hg, and or proteinuria (≥5 g/24 hours [or ≥4+ urine dipstick], and/or platelet count ≤100 000 cells/µL.
§Measurements of SDMA concentrations (including SDMA quality controls) were performed in a subgroup of 60 women (36 cases, 24 controls).

mester at delivery), severity of pre-eclampsia, gestational age at delivery, and birth weight (Table 1) were comparable with those from previous studies from Western Europe.[2,3,5] In light of the lack of ethnicity-related differences in ADMA concentrations in our sample, ethnicity does not appear to explain our results.

Thus, our results support the hypothesis that pre-eclampsia in low- and high-risk populations may have distinct underlying causes.

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Funding/Support: Financial support to the VILANO group and the Pregeno project was provided by COLCIENCIAS (Colombia).

Acknowledgment: We thank Mariola Kastner and Anna Steenpaß for excellent technical assistance, and the midwives and the pregnant women who participated in this study.

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CORRECTION

Incorrect Data in Table: In the Original Contribution entitled "Comparison of Screening Mammography in the United States and the United Kingdom" published in the October 22/29, 2003, issue of THE JOURNAL (2003;290:2129-2137), there were incorrect data in Table 5 due to rounding errors. On page 2134, for cancer detected for women aged 50 to 59 years, the rate per 1000 women of 24.5 should have been 24.8 for BCSC and 19.4 should have been 19.2 for NHSBSP, and for cancer detected in women aged 60 to 69 years, the rate per 1000 women of 31.5 should have been 31.6 for BCSC and 26.6 should have been 27.2 for NBCCEDP.