Letter to the Editor

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Evidence Supporting a Beneficial Role for Long-Term L-Arginine Supplementation in High-Risk Pregnancies

To the Editor:

In the March issue of *Hypertension* Noris et al describe that preeclamptic women have decreased placental villi L-arginine concentration and overexpression of arginase II.[1] In February, Alexander et al reported that supplementing L-arginine in pregnant rats with reduced uterine perfusion decreased blood pressure, concomitantly increasing serum L-arginine levels and urinary nitrite/nitrate.[2] Both reports highlight the role of the L-arginine–nitric oxide (NO) pathway in determining normal and preeclamptic pregnancies and sustain the potential benefit of L-arginine supplementation in women at risk of preeclampsia. Although L-arginine has been given acutely to preeclamptic women, there is no concordance about its benefits.[3,4] We wish to underscore the benefits of this intervention with our experience with chronic long-term oral L-arginine supplementation in women at risk of placentation-related disorders.

Seventeen women with bilateral notching and high uterine artery resistance in transvaginal ultrasounds performed 2 weeks apart (−2 and 0 weeks) were included. Endothelial function was also assessed by high-resolution ultrasound of the brachial artery. Of the 15 multiparas, 3 had presented preeclampsia associated with stillbirth in 2, 5 had unexplained recurrent abortions, 2 had isolated spontaneous abortions, and 1 had a premature delivery of ischemic origin. None presented thrombophilias. L-Arginine supplementation (0.1 g/kg per day PO; Smartbasics, San Francisco, Calif) was started at 10.1±0.9 (SEM) weeks of gestation (week 0), and continued until delivery. After 2 weeks on L-arginine, the women's mean arterial pressure and uterine artery resistance index decreased (75±2 versus 82±3 and 80±2 mm Hg; 0.76±0.01 versus 0.89±0.02 and 0.87±0.01 and at −2 and 0 weeks respectively; $P<0.05$ for 2 versus 0 and −2 weeks for both values), and endothelial-mediated vasodilatation improved (10.9%±1.0% versus 7.7%±1.9% and 5.5%±1.2%; $P<0.05$ for 2 versus −2 weeks). All women delivered at term (38.0±1.1 week), and excepting 1, had infants of normal weight (3227±371 g); one woman developed a moderate preeclampsia ($\chi^2=12.5$, $P<0.001$ for the combination of live births, perinatal outcome, and preeclampsia versus the preceding pregnancy). Maternal tolerance to supplementation was adequate; the offsprings presented no side effects at birth or during 2 to 48 months follow-up.

Our data show that the acute enhancement of the L-arginine–NO pathway ameliorates the local and systemic adaptations of pregnancy. While the improvement of the perinatal outcome could represent a spontaneous remission, a beneficial effect of L-arginine is suggested, because 9 out of 17 women previously presented 2 or more placentation-related complications of pregnancy, and patients with this clinical history have recurrence rates of preeclampsia or pregnancy loss of 40% to 60%, respectively. Moreover, all women included in this intervention presented in early pregnancy bilateral notching of the uterine arteries, index associated to odds ratio of 42.02, 8.61, and 2.38 for preeclampsia, fetal growth restriction, and premature delivery, respectively.[5] Thus, these data support the recommendation of performing trials with L-arginine supplementation given by Noris and Alexander.

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