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**First trimester elevation in circulating endothelin-1 and arterial stiffness are predictive of late pregnancy preeclampsia**

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Preeclampsia (PE) is characterized by late pregnancy hypertension and proteinuria. PE causes significant morbidity for the maternal-fetal unit. Circulating endothelin-1 (ET-1), a potent vasoconstrictor, is elevated at the time of diagnosis of human PE. In addition, women with PE demonstrate arterial stiffness as early as the end of the first trimester. However, it is unknown if arterial stiffness is associated with a first trimester elevation in ET-1 and post-delivery placental ET-1. We

hypothesized that 1) first trimester plasma ET-1 is elevated and is associated with arterial stiffness in women who develop PE; 2) first trimester ET-1 is predictive of PE; and 3) placental ET-1 is increased in PE. To address these questions, we performed a nested case-control study in women at risk for PE. First trimester plasma ET-1 was measured via ELISA; aortic stiffness and carotid beta-stiffness (C $\beta$ S) were measured by carotid-femoral pulse-wave velocity (CFPWV)

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and carotid tonometry/ultrasound, respectively. While the maternal age of controls (n=126; age  $30 \pm 0.45$  years) and PE (n=15; age  $31 \pm 1.3$  years) were similar, the PE group had a higher first trimester BMI ( $35 \pm 3$  vs.  $29 \pm 1$  kg/m<sup>2</sup>,  $p = 0.01$ ), systolic ( $125 \pm 2$  vs.  $113 \pm 1$  mmHg,  $p < 0.01$ ) and diastolic blood pressure ( $68 \pm 2$  vs.  $60 \pm 1$  mmHg,  $p < 0.01$ ) compared with controls. In addition, first trimester plasma ET-1 ( $2.7 \pm 0.4$  vs.  $2.0 \pm 0.2$  pg/mL,  $p < 0.01$ ), CFPWV ( $7.2 \pm 0.5$  vs.  $6.1 \pm 0.2$  m/s,  $p = 0.016$ ), and C $\beta$ S ( $8.4 \pm 1.9$  vs.  $6.3 \pm 0.3$ ,  $p = 0.055$ ) were higher in the PE group. Consistent with previous studies, third trimester plasma ET-1 was elevated in the PE group ( $2.9 \pm 1.1$  vs.  $1.6 \pm 0.1$  pg/mL,  $p < 0.01$ ) which paralleled a 2.5 fold increase in placental decidual ET-1 mRNA ( $p < 0.0001$ ). ROC analyses showed that first trimester plasma ET-1 (AUC=0.71,  $p < 0.001$ ) and CFPWV (AUC=0.70,  $p=0.014$ ) were predictive of PE. This study supports the novel concept that elevated ET-1 in preeclampsia begins early in the first trimester and is associated with premature arterial stiffness. Further, these novel data suggest that ET-1 may play an important role in the first trimester prediction and pathogenesis of preeclampsia.

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