ELABELA concentration is not decreased in maternal plasma before the onset of preeclampsia

OBJECTIVE: ELABELA (ELA), an endogenous ligand for the apelin receptor (APLR), is a peptidic hormone expressed both by the kidneys and placenta. Via the endothelial receptor APLR, secretion of ELA seems to be critical for mouse placental angiogenesis and endothelial tipping.[1] In gravid mice carrying ELA-deficient embryos, placental insufficiency of vascular origin and hallmarks of preeclampsia [PE] are present.[1] However, the level of current evidence linking the human maternal preeclamptic phenotype to maternal blood soluble form of VEGF-R1 (sflt1) increase is so high, and the hypoxic RNA signal in ELA-deficient placentas so strong, that the lack of sFlt1 increase, at the protein level, in the murine model is puzzling. Two human studies subsequently found no ELA decrease in maternal blood, either at delivery in women with preterm PE (mean gestational ages, 29.4 and 30.8 weeks),[2,3] or in late-onset PE (mean gestational age, 37.6 weeks), whereas ELA was actually increased.[3] Given these contradictory findings and the claim that ELA acts independently and earlier than sFlt1,[1] we investigated whether ELA was dysregulated before PE onset.

MATERIALS AND METHODS: We randomly selected 26 nulliparous women enrolled in the MOrbiMortality Amelioration (MOMA) trial; 12 with PE, 14 with normal pregnancy (NP). MOMA (NCT00763672) was a randomized controlled trial (2008 to 2011) on the effects of close monitoring of women identified to be at high risk for PE on the basis of an increased sFlt-1 plasma assayed before 29 weeks' gestation. Controls were NP women with at-term delivery and no maternal pathology. PE was defined as the onset of hypertension (systolic or diastolic blood pressure ≥140 or ≥90 mm Hg, respectively) and proteinuria (≥300 mg/L or ≥300 mg/d) after 20 weeks' gestation. All participants gave written informed consent, including for prospectively requested plasma samples archived for future ancillary studies to assess nongenetic biomarkers for PE. The study protocol was approved by the ethics committee (Comité de Protection des Personnes [CPP]) Paris, France, on May 7, 2008.

Concentrations of ELA in maternal plasma were measured in duplicate by enzyme immunoassay (Human ELABELA ELISA kit; Creative Diagnostics, NY) with a detection range of 0−100 ng/mL. Our findings gave an intra-assay coefficient of variation of 30%; the kit is 100% specific for human ELA-32 and ELA-21 isoforms. Concentrations of sFlt1 were measured in duplicate by solid-phase quantitative sandwich immunoassay (Human VEGFR1/Flt1 Quantikine ELISA Kit; Quantikine R&D Systems Inc, Minneapolis, MN). Results are given as mean value ± standard deviation. Statistical comparison of concentrations was made using the nonparametric Mann−Whitney test.

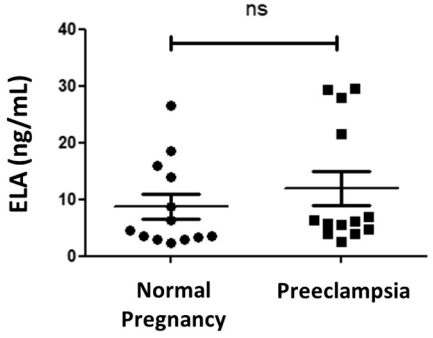
RESULTS: Mean systolic blood pressure was 159 ± 22 and 127 ± 7 mm Hg for the PE and NP groups, respectively, at the time of delivery; mean diastolic blood pressure was 98 ± 10 and 77 ± 6; and mean proteinuria was 1.1 ± 0.7 and 0 ± 0 g/d. Mean gestational age at blood sampling was 170 ± 9 and 174 ± 8 days for the NP and PE groups, respectively.

Mean ELA concentration was 11.86 ± 10.8 vs 8.71 ± 7.7 ng/mL ($P = .25$) (Figure), and mean sFlt-1 concentration was 4192 ± 2771 and 2291±923 ng/mL ($P = .08$) in the PE and NP groups, respectively. There was no statistical correlation between ELA and sFlt-1 concentrations.

CONCLUSION: In line with 2 recent studies, our study does not support the hypothesis that human PE is characterized by an early deficiency in ELA. We do not question the role of ELA in the physiology of placental angiogenesis, or deny that there is a relative ELA deficiency in the feto-maternal unit. However, we question whether the custom-made enzyme-linked immunosorbent assay (ELISA) accurately measured ELA in murine maternal blood. Of note, using the same ELISA kit, both the Pritchard et al[2] and Panaitescu et al[3] studies found different ELA concentrations in samples collected at term (~30 pg/ml and 5 ng/ml, respectively, corresponding to a ratio of approximately 5000). Using a different ELISA, our results are similar in range to those from Panaitescu et al (~10 ng/mL). These contradictory results also suggest variances in the specificity of ELABELA tests from different manufacturers. More studies are also needed to identify whether specific ELABELA isoforms are dysregulated before the diagnosis of preeclampsia. ■

FIGURE

ELABELA (ELA) concentrations in maternal plasma sampled before 29 weeks' gestation from women with a final diagnosis of preeclampsia or of normal pregnancy



ns, Not significant.

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Evaluation of proposed criteria for research reporting of amniotic fluid embolism

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OBJECTIVE: To examine the diagnostic performance of proposed criteria for the research reporting of amniotic fluid embolism (AFE).[1]

STUDY DESIGN: The Amniotic Fluid Embolism Registry is an international database established at Baylor College of Medicine in partnership with the Amniotic Fluid Embolism Foundation and the Perinatal Research Branch of the Division of Intramural Research of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health. Charts submitted to the registry between August 1, 2013, and June 31, 2017, underwent 2 separate analyses. First, a group of maternal–fetal medicine specialists with expertise in critical care (S.L.C., G.A.D., M.A.B.) conducted a detailed analysis of medical records to categorize these women into 3 groups, based on their consensus diagnosis: (1) AFE; (2) a distinct diagnosis other than AFE; and (3) indeterminate/uncertain diagnosis. Next, each chart was independently analyzed by a physician with no obstetric training to determine whether the medical record did or did not contain each of the recently published criteria for the diagnosis of AFE[1] (Table). Agreement between expert record analysis and the presence of these strict, objective criteria was determined.

RESULTS: A total of 115 charts were reviewed. Expert review resulted in a diagnosis of AFE in 68 cases (59%), a clear alternative diagnosis in 26 cases (23%), and an indeterminate diagnosis in 21 cases (18%) (Figure). When analyzed according to the

TABLE
Uniform diagnostic criteria for research reporting of amniotic fluid embolism[1]

1. Sudden onset of cardiorespiratory arrest, or both hypotension (systolic blood pressure <90 mm Hg) and respiratory compromise (dyspnea, cyanosis, or peripheral capillary oxygen saturation [SpO2] <90%)
2. Documentation of overt disseminated intravascular coagulation (DIC) following appearance of these initial signs or symptoms, using scoring system of Scientific and Standardization Committee on DIC of the International Society on Thrombosis and Haemostasis (ISTH), modified for pregnancy. Coagulopathy must be detected prior to loss of sufficient blood to itself account for dilutional or shock-related consumptive coagulopathy
3. Clinical onset during labor or within 30 min of delivery of placenta
4. No fever (≥38.0°C) during labor

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