Have investigators reached the first steps for redefining a diagnostic definition of preeclampsia that includes morbidity?

Yes. In this cohort of nationally representative hypertensive pregnancies, Thadhani et al define a sFlt-1/PlGF ratio that predicts morbidity within 2 weeks of admission. This could revolutionize the clinical diagnosis of preeclampsia.

Thadhani R, Lemoine E, Rana S, et al. Circulating angiogenic factor levels in hypertensive disorders of pregnancy. N Engl J Med. 2022;1. DOI: 10.1056/EVIDoa2200161

FAST TRACK

Both sFlt-1 and PlGF have been mooted for almost 2 decades as potential predictive, if not diagnostic, aids with respect to preeclampsia

EXPERT COMMENTARY
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The standard core lecture on preeclampsia given to all medical students frequently begins with an epic, if not potentially apocryphal, statement regarding how this disease has been noted in the annals of medical history since the time of the Ancients. Although contemporary diagnostic criteria for preeclampsia are not that far out of date, they are close. The increased urinary protein loss and hypertension preceding eclamptic seizures was first noted at the end of the 19th century. The blood pressure and proteinuria criteria used for diagnosis was codified in its contemporary form in the late 1940s. Since then, "tweak" rather than "overhaul" probably best describes the updates of the obstetrical community to the definition of preeclampsia. This has just changed.

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Details of the study

Thadhani and colleagues prospectively recruited a nationally representative observational cohort of patients hospitalized for hypertension during pregnancy, then followed the patients until either the diagnosis of preeclampsia with severe features or for 2 weeks, whichever came first. At enrollment, circulating levels of the soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF) were measured. In a 2-phased design, the first 219 participants were used to define a sFlt-1/PlGF ratio that would predict progression to severe preeclampsia within 2 weeks. The next 556 enrollees served to validate the predictive properties of the ratio. The authors found that a sFlt-1/PlGF ratio of ≥40 predicted progression to preeclampsia with severe features with an area under the curve (AUC) of 0.92.

As products of the trophoblasts, both sFlt-1 and PlGF have been mooted for almost 2 decades as potential predictive, if not diagnostic, aids with respect to preeclampsia. Indeed, both analytes are commercially available in Europe for specifically this purpose and many maternal-fetal medicine practitioners working in the European equivalent American tertiary referral centers use an sFlt-1/PlGF

ratio as their primary criteria for a diagnosis of preeclampsia. Within the United States, there was an initial flurry of interest in and an infusion of corporate and federal research support for sFlt-1 and PlGF as diagnostic aids for preeclampsia in the mid-2000s. However, at present, the US Food and Drug Administration (FDA) has not sanctioned these (or any) biomarkers to aid in the diagnosis of preeclampsia. As Thermo-Fisher Scientific (Waltham, Massachusetts) is a supporting partner in this study, it is almost certain that these data will be submitted for review by the FDA as part of an application for a preeclampsia diagnostic. At some point in the near future, American practitioners will potentially be able to join their European colleagues in utilizing these biomarkers in the diagnosis of preeclampsia with severe features. ●

WHAT THIS EVIDENCE MEANS FOR PRACTICE

Thadhani and colleagues observed that the majority of both maternal and neonatal morbidity in their study, including 8 of the 9 neonatal deaths and both cases of eclampsia, occurred among patients with a ratio ≥40 at admission. There was an inverse relation between the sFlt-1/PlGF ratio and the admission to delivery interval. Where only 17% of patients in the highest quartile of ratios remained pregnant at 14 days post-enrollment, more than 79% of the lowest quartile were still pregnant. If not a causal relationship, sFlt-1 and PlGF are clearly associated with not only the occurrence of preeclampsia with severe features but also the degree of morbidity.

The implication for the disposition of patient care resources is clear. Patients at higher risk for preeclampsia could be seen in specialty high-risk clinics with an emphasis on increased monitoring. In situations where tertiary care is more remote, plans could be developed should they need to be transported to centers able to provide the appropriate level of care. Conversely, patients screening at lower ratios may be more appropriately managed as outpatients, or at least in less clinically involved accommodations.

Thadhani et al do note that there were false negative cases in which the sFlt-1/PlGF ratio at admission was <40 but patients nonetheless progressed to preeclampsia with severe features. The majority of these cases had concurrent pre-pregnancy, chronic hypertension. This observation suggests not only the potential for insights into the pathophysiology of the hypertensive diseases in pregnancy but also that the interpretation of the sFlt/PlGF ratio may eventually need to be stratified by preexisting conditions.

The final implications for the observations of this study are perhaps the most tantalizing. If there is a causal relation between the level of the sFlt-1/PlGF ratio and the morbidity of preeclampsia with severe features, then lowering the circulating concentration of sFlt-1 would ameliorate not only the morbidity but also the risk of preeclampsia. Work with plasma phoresies has suggested that this might be possible, albeit via a clinical intervention demanding more intensive resources. The potential for a targeted pharmacologic moderation of sFlt-1 levels would hold great promise in that those identified as at increased risk could be offered an intervention widely available to all.

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