CIRCULATING ANGIOGENIC FACTOR LEVELS IN HYPERTENSIVE DISORDERS OF PREGNANCY

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INTRODUCTION

Hypertensive disorders in pregnancy (HDPs), defined as prepregnancy (chronic) or pregnancy-associated hypertension, are common pregnancy complications. HDPs are strongly associated with severe maternal complications, such as heart attack and stroke, and are a leading cause of pregnancy-related death. Among women with hypertensive disorders of pregnancy, biomarkers may stratify risk for developing preeclampsia with severe features (sPE).

Material and Methods. In 18 U.S. centers scientists prospectively measured the ratio of serum soluble fms-like tyrosine kinase 1 (sFlt-1) to placental growth factor (PlGF) in pregnant women hospitalized between 23 and 35 weeks of gestation. The primary outcome was predicting sPE, and secondary outcomes included predicting adverse outcomes within 2 weeks. The prognostic performance of the sFlt-1:PlGF ratio was assessed by using a derivation/validation design.

Analysis. The primary aim was to derive and validate the prognostic performance of the sFlt-1:PlGF ratio to predict the development of sPE within 2 weeks. Participants presenting with sPE at enrollment were excluded; the remaining participants constituted the primary study population. In the derivation cohort, scientists identified the cutoff value of the sFlt-1:PlGF ratio that provided the highest sensitivity while assuring a minimum specificity of 70%. In the validation cohort, the hypothesis that sensitivity and specificity were at least 70% was tested with 95% Wilson confidence intervals (CIs). Furthermore, the discrimination ability of biomarkers was quantified by using area under the receiver-operating characteristic curve (AUC) with 95% CIs, comparing the sFlt-1:PlGF ratio versus routinely assessed measures: systolic and diastolic blood pressures, liver and kidney function tests, and platelet counts.

Discussion. Derivation cohort. Thirteen hospitals participated in the derivation cohort. Of the first 299 enrolled participants, 79 (26%) met the criteria for sPE at admission and were excluded. The incidence of sPE within 2 weeks was 31.3%. The median sFlt-1:PlGF ratio differed between women who developed sPE within 2 weeks (200; interquartile range, 53 to 458) and those who did not (6; interquartile range, 3 to 26; $P<0.001$). Restricting the study to only one enrollment per patient (first or last enrollment) yielded similar findings.

An sFlt-1:PlGF ratio of ≥40 provided prognostic performance estimates of 81% sensitivity (95% CI, 70 to 90) and 81% specificity (95% CI, 74 to 87). At this cutoff, the positive predictive value was 66% (95% CI, 55 to 76) and the negative predictive value was 90% (95% CI, 84 to 95) for the primary outcome. The performance of this discriminatory ratio was then further tested in the validation cohort.

Valiation cohort. Women in the validation cohort were enrolled at all 18 hospitals and resembled those in the derivation cohort. Of the 715 enrollments, 159 (22%) met the criteria for sPE at admission and were excluded. The incidence of sPE within 2 weeks was 33.5%. Median sFlt-1:PlGF ratios were consistently elevated in women who developed sPE, a finding evident at all clinical sites. Women who developed sPE had sFlt-1:PlGF ratios approximately 40 times higher than those who did not (291 [interquartile range, 121 to 777] versus 7 [interquartile range, 3 to 40], respectively; P<0.001). Findings were similar when the analysis was restricted to only one (first or the last) enrollment per patient.

Based on these data, scirntists concluded that an sFlt-1:PlGF ratio ≥40, when both sFlt-1 and PlGF are measured in picograms per milliliters, provided a prognostic performance of 94% sensitivity (95% CI, 89 to 96) and 75% specificity (95% CI, 70 to 79), and yielded a positive predictive value of 65% (95% CI, 59 to 71) and a negative predictive value of 96% (95% CI, 93 to 98) for the primary outcome. Restricting the analysis to women with a history of chronic hypertension (n=313), the sFlt-1:PlGF ratio ≥40 yielded positive and negative predictive values of 59% (95% CI, 50 to 67) and 94% (95% CI, 90 to 97), respectively. Similarly, in the subgroup of patients who identified as Black race (n=169), the ratio ≥40 yielded positive and negative predictive values of 66% (95% CI, 51 to 67) and 99% (95% CI, 94 to 100). Race-specific multiples of the median of the sFlt-1:PlGF ratio were also higher for Black women compared with White or Asian women.

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