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Et al.

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Abstract:

Preeclampsia is a multi-system disorder characterized by hypertension, edema and proteinuria affecting between 5-10% of pregnancies. A subset of cases progress to severe preeclampsia with exacerbated hypertension/proteinuria and evidence of nervous system, liver and/or kidney dysfunction, in addition to fetal growth restriction. Soluble fms-like tyrosine kinase-1 (sFlt) is minimally expressed in many tissues, including the placenta, and is a circulating antagonist to vascular endothelial growth factor. With progression of pregnancy, sFlt levels significantly rise, especially in women who develop preeclampsia. Diagnostic tests to predict preeclampsia in pregnant women are limited and current tests measure total sFlt in relationship to placental growth factor with varying sensitivity and specificity. We hypothesized that a pregnancy-specific splice variant of sFlt (sFlt1-14), almost exclusively expressed by the placenta, would serve as an improved serum biomarker for the development of preeclampsia. Monoclonal antibodies (mAbs) were developed that specifically bind the two predominant isoforms of sFlt (sFlt1 and sFlt1-14) by hybridoma generation from wild type mice immunized with c-terminal peptides of the two isoforms. Western blot, ELISA and affinity analysis indicated the mAbs were specific for sFlt1 or sFlt1-14 splice variants and recognized these proteins in biological fluids (amniotic fluid or serum). A quantitative capture ELISA was developed whereby total sFlt in biological fluid is captured by a unique human mAb and specific levels of sFlt1 or sFlt1-14 are detected by their respective mouse mAb, followed by anti-murine secondary antibody development. Using recombinant sFlt1 or sFlt1-14 as standards, these endogenous proteins were quantified in commercially available third trimester human pregnant sera. Future studies will measure these isoforms in sera prospectively collected from women with known outcomes of a healthy pregnancy or preeclampsia and the ability of absolute quantitation of the isoform(s) or a ratio of the two to predict the likely onset and severity of preeclampsia will be evaluated.