Role of Angiogenic Factors in Preeclampsia

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Preeclampsia, the syndrome of hypertension, proteinuria, edema and hyperuricemia occurring during the last trimester of pregnancy remains one of the great mysteries. Recently gene expression profiling of placental tissue from healthy and preeclamptic women used to see which genes were up or down regulated in preeclamptic patients. Alterations in circulating angiogenic proteins correlated with disease severity, earlier onset of preeclampsia and birth of small for gestational age (SGA) fetus. These findings lend support to the hypothesis that circulating angiogenic proteins may have an important biological role in preeclampsia.

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Preeclampsia disappeared after delivery, suggesting that the factor may be released by the placenta. Thus the antiangiogenic effects of sFlt-1 may account for many of the manifestations of preeclampsia including the unique glomerular effects. There is evidence from animal model that VEGF is important in maintaining glomerular endothelial cell health and healing. In antiangiogenic oncology trial, antagonism of VEGF using neutralising antibodies and VEGF receptor inhibitor can produce headache, hypertension, proteinuria and coagulopathy in human subjects. Therefore by neutralising VEGF and PIGF, excess sFlt-1 may have a contributory role in the pathogenesis of the maternal syndrome of preeclampsia. The hypothesis that excessive production of sFlt-1 may play a causal role in the preeclampsia is supported by recent studies that reported a link between trisomy 13 pregnancies and circulating angiogenic protein concentrations during the first and second trimester. Fetuses with an extra copy of this chromosome should theoretically produce more of these gene products than their normal counterparts. The ratio of circulating sFlt-1 to PIGF was recently shown to be significantly increased in these women thus accounting for the increased risk of preeclampsia.

Endoglin a co-receptor for transforming growth factor $\beta_1$ and $\beta_2$ (TGFB$\beta_1$/TGFB$\beta_2$) is highly expressed on the cell membrane of vascular endothelium and syncytotrophoblast. Placental endoglin is up-regulated in preeclampsia, releasing soluble endoglin into maternal circulation. Soluble endoglin is an antiangiogenic protein that may inhibit TGF-$\beta$, signaling in vasculature. Adenoviral mediated overexpression of both sFlt-1 and soluble endoglin caused severe vascular damage, nephrotic range proteinuria, severe hypertension, a syndrome similar to the HELLP syndrome. Along with experimental evidence in rodents, these data suggest that circulating soluble endoglin and sFlt-1, each of which causes endothelial dysfunction by a different mechanism, may both contribute to the syndrome of preeclampsia. How placental dysfunction is related to placental sFlt-1 production and why placental perfusion is deranged in preeclampsia remains unknown. Recent data of in vitro primary cytotrophoblast cultures suggest that placental hypoxia may play an important role in up regulating sFlt-1 production and this up regulation of sFlt-1 may be through genetic, environmental or immunological.

The next step is, will measurement of blood sFlt-1, VEGF and PIGF levels allow us to develop a test that can predict the development of preeclampsia before the onset of symptoms. Few studies have concentrated on examining the potential ability of sFlt-1 and PIGF level as biomarkers in the diagnosis and prediction of preeclampsia. Most of the studies have looked statistically at sFlt-1 as a potential predictor of preeclampsia. Examining odd ratios, sensitivity and specificity for various sFlt-1 cut off values in different trimesters has yielded the conclusion that higher the sFlt-1 levels the more predictive it is of preeclampsia. PIGF a smaller protein is decreased in the urine of women with preeclampsia compared with normal pregnancy. Similar to serum PIGF, urinary levels were lowest in the preeclampsia group with active disease regardless of gestational age at the time of onset of symptoms. It was concluded that urinary PIGF concentration during mid pregnancy was low only in the setting of preeclampsia. When urinary PIGF was combined with a serum sFlt-1 and PIGF ratio (ratio>10 suggesting preeclampsia), all of the cases destined to develop preeclampsia within the following 5 weeks could be distinguished from the control pregnant women. Thus a two-step approach of initial urinary screening of PIGF followed by serum sFlt-1/PIGF in the women who have low urinary PIGF levels may be a cost-effective approach for the screening of preeclampsia. If a reliable and valid urinary dipstick assay can be developed, one scenario might be to screen all women for detection of low urinary PIGF concentration. Among those with low levels, serial serum measurements of sFlt-1 and PIGF could then be used to identify more precisely the individual at high risk of developing pre-eclampsia. Prospective longitudinal studies with measurements throughout pregnancy are needed to assess the validity of observations.

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REFERENCES