21 CIRCULATING CONCENTRATIONS OF ANGIOGENIC FACTORS TO PREDICT EARLY DELIVERY IN PREECLAMPSIA BEFORE 34 WEEKS

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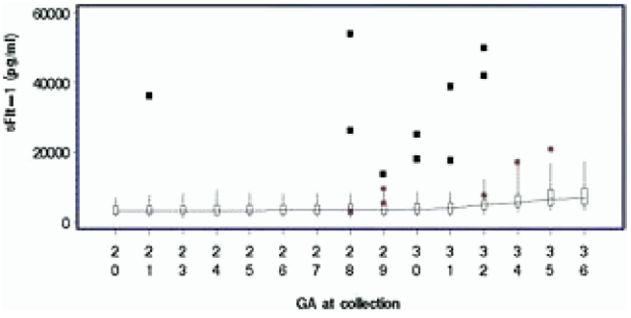
OBJECTIVE: To determine whether after onset of preeclampsia (PE) before 34 wks serum concentrations of soluble fms-like tyrosine kinase 1 (sFlt1), soluble endoglin (sEng), and placental growth factor (PlGF) can predict early delivery.

STUDY DESIGN: Angiogenic factors were measured in 5501 samples obtained from 2200 nulliparas before onset of gestational hypertension or PE. Samples at each GA wk were augmented with samples from the preceding and following wk to determine the concentration range in normotensive women for that GA wk. Concentrations in samples obtained after onset of disease from 107 women with PE were compared to the normotensive GA wk-specific distributions. PE onset was the time of the first measurement leading to diagnosis.

RESULTS: Of 107 women with PE, 16 developed PE before 34 wks. Among them, sFlt1 exceeded the 99th percentile of the normotensive range in 10 of 10 delivered before 34 wks vs 0 of 6 delivered beyond 34 wks ($P<0.001$). Corresponding numbers for sEng were 8 of 10 vs 2 of 6 ($P=0.12$); and for PlGF below the 1st percentile, 7 of 10 vs 2 of 6 ($P=0.30$). The interval between PE onset and delivery for women delivered before 34 wks was 2.4 - 27.3 days.

CONCLUSION: Serum sFlt1 may be useful for managing women with PE onset before 34 wks. If these findings are confirmed, women with levels above the 99th percentile of the normotensive range should be considered for administration of steroids and delivery.



Serum sFlt1 by GA Week of Collection in Normotensive Women (box 25-75 percentiles, whiskers 5-95 percentiles) and Women with PE <34 Wks [delivery <34 Wks (filled squares); >=34 Wks (filled circles)]

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22 INCREASED SENESCENCE AND REDUCED FUNCTIONAL ABILITY OF FETAL ENDOTHELIAL PROGENITOR CELLS IN PREGNANCIES COMPLICATED BY PREECLAMPSIA WITHOUT INTRAUTERINE GROWTH RESTRICTION

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OBJECTIVE: Recent morphologic studies of preeclampsia-affected placentas have shown irregular and narrow lumina on fetal placental capillary and increased branching angiogenesis in chorionic villi. Depletion and functional impairment of circulating endothelial progenitor cell (EPC) is associated with diseases related to endothelial dysfunction. The aim of this study is to investigate the number and functional status of fetal EPCs in pregnancies complicated by preeclampsia without intrauterine growth restriction (IUGR).

STUDY DESIGN: Fetal EPCs were isolated, characterized, and counted from 17 women with preeclampsia without IUGR and 30 gestational age-matched normotensive pregnant women. After ex vivo cultivation and differentiation, colony forming assay and differentiation time assay were performed to detect functional activity of the cells. In addition, to assess cellular senescence, senescence-associated β-galactosidase (SA-β-gal) staining for EPCs was executed and the staining density was detected by densitometry.

RESULTS: The number of circulating fetal EPCs was significantly lower in the preeclamptic pregnancy compared with normal pregnancy (6.3 ± 2.2 vs. $4.1 \pm 1.8 \times 105/50ml$, $p<0.001$). Compared with normal pregnancy, differentiation time from EPC to outgrowing cell was longer ($p<0.001$), and the number of colonies after differentiation was smaller in preeclampsia ($p<0.001$). The intensity of SA-β-gal staining was higher in preeclamptic pregnancy ($p<0.001$).

CONCLUSION: This study shows that the number and functional ability of fetal EPCs in pregnancies complicated by preeclampsia are significantly decreased and more senescent compared to those of normal pregnancy. Such impairment may be associated with fetal endothelial dysfunction. And these alterations of fetal EPCs may give an explanation for placental dysfunction in preeclamptic condition.

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23 CHRONIC NITRIC OXIDE INHIBITION IN A RAT MODEL OF PREECLAMPSIA (PE) LEADS TO URINARY PROTEOMIC BIOMARKER SIGNATURES SIMILAR TO HUMANS

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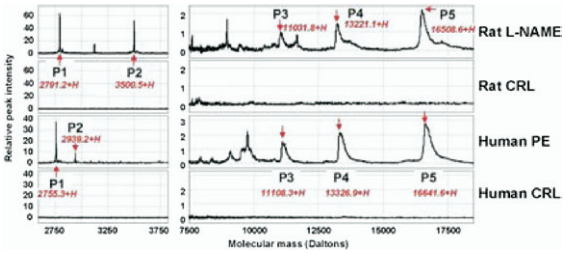
OBJECTIVE: Urine proteomic profiling identified specific non-random N-terminus cleavage fragments of albumin as biomarkers characteristic of severe PE. Chronic NO inhibition in rats produces a PE-like syndrome (hypertension, proteinuria). We investigated whether NO blockade induces changes in the rat urine proteomic profile comparable to that observed in women with PE.

STUDY DESIGN: Osmotic pumps delivering saline (CRL; n=10) or L-NAME 50 mg/rat/day (LN; n=14) were inserted on d17 of gestation (term=d22). Animals were sacrificed on d21. Urine was obtained by trans-vesical aspiration. SELDI mass spectrometry and de-novo sequencing in MS/MS mode was used for proteomic profiling and biomarker identification. Validation experiments included urine and serum ELISA for albumin and sFlt-1. Urine SELDI tracings from women with severe PE (n=10) and normotensive controls (n=10) were used for comparison. Bioinformatics was used to identify similarity/dissimilarity between human and rat.

RESULTS: LN rats had IUGR pups ($p<0.001$), higher urinary albumin ($p<0.001$) and plasma sFlt-1 ($p=0.01$) levels compared with CRL. Plasma sFlt-1 levels correlated with urinary albumin levels ($r=0.5$, $p<0.01$). 5 biomarkers were exclusively present in LN rats (P1-P5, Figure). MS/MS identified the rat biomarkers as fragments of albumin. ***In silico*** analysis located cleavage sites in identical positions to those seen in humans: P1 corresponded to the first N-terminal 24 aa of rat (2790 Da) and human albumin (2754 Da).

CONCLUSION: In the rat PE-like syndrome, the urine proteomic signature generated by specific fragments of albumin is similar to that seen in humans, thereby emphasizing the relevance of this model for the pathogenesis of human PE.



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24 CEREBRAL WHITE MATTER LESIONS IN FORMERLY (PRE)-ECLAMPTIC WOMEN

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OBJECTIVE: The pathophysiologic mechanisms of the neurologic disturbances in (pre)-eclampsia are poorly understood. Particularly elusive is the association of hypertension with grand mal seizures and brain lesions characterized histopathologically by (sub)cortical edema, petechial hemorrhages and infarctions. This is made even more enigmatic because eclamptic women generally appear to have full clinical recovery. Previously we have shown that six weeks post partum approximately 25% of eclamptic women show persistent cerebral white matter lesions (WML) on MRI. The aim of the present study was to refute or confirm the persistence of such cerebral WML in the long term.

STUDY DESIGN: 39 formerly eclamptic, 35 formerly preeclamptic and 31 normotensive parous women were matched for age and elapsed time since the index pregnancy. (Pre)-eclampsia was defined according to international standards. Participants underwent T1, Proton Density, Flair and T2-weighted MRI scans (3 Tesla). The scans were rated for presence of WML by a radiologist blinded for patient category. Presence of WML was tested with Chi-square, alpha was set at 0.05.

RESULTS: Significantly more women in the formerly (pre)-eclamptic group demonstrated subcortical WML compared to the control group (35% vs. 19%, $P<0.001$). Average age in the control group was similar to formerly (pre)-eclamptic women (38 ± 7 vs. 39 ± 6 years, respectively, $P=0.64$). Elapsed time since the index pregnancy was also similar in both groups (5.4 ± 4.2 control vs. 6.8 ± 4.5 (pre)-eclampsia, $P=0.12$).

CONCLUSION: Several years after a pregnancy complicated by (pre)-eclampsia almost twice as many women show WML on MRI compared to women with a normotensive pregnancy. It is thought that the neurological disturbances in (pre)-eclampsia represent a form of Posterior Reversible Encephalopathy Syndrome. However, this entity seems a misnomer since such lesions are not necessarily reversible. The current belief that the neurological disturbances in (pre)-eclampsia represent a one-time event should be revised. Long-term clinical consequences need to be determined.

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