9 FIRST TRIMESTER MULTI-ANALYTE SCREENING FOR PLACENTAL DEVELOPMENT

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OBJECTIVE: To examine 1st trimester relationships between maternal characteristics, placental Doppler studies and serum markers of placental angiogenesis (Angiopoietin-2, ANG-2, Placental growth factor, PIGF), placental mass (pregnancy associated protein-A, PAPP-A, placental protein-13, PP-13, free beta HCG) and inflammation (Pentraxin-3, PTX-3).

STUDY DESIGN: Prospectively enrolled patients at 11-14 weeks had serum ANG-2, PIGF, PAPP-A, PP-13 and PTX measured by ELISA. Levels of markers were correlated to each other and related to gestational age (GA), maternal age, race, body mass index (BMI), mean arterial blood pressure (MAP), nicotine/caffeine use as well as measures of uterine and umbilical artery blood flow resistance.

RESULTS: 111 consecutive patients completed the multi-analyte screen. ANG-2 correlated with PIGF and pp-13 (Pearson 0.484, 0,326). PP-13 correlated with free betaHCG (Pearson 0.386, all $p<0.0001$). ANG-2 and pp-13 were the only factors related to BMI, while ANG-2 showed the stronger relationships MAP than PIGF. Smoking had a significant impact on PP-13 levels and only PIGF was related to placental Doppler studies (table stars indicate significant relationships *=$p<0.05$, **=$p<0.001$). PTX-3 had no significant relationships with any study parameter.

CONCLUSION: Of the maternal serum analytes that reflect placental angiogenesis ANG-2 relates most to maternal vascular risk factors while PIGF levels show closer relationship with placental blood flow resistance. PP-13 acts as a marker of placental mass illustrating the effects of smoking in the first trimester. These independent relationships suggest a potential benefit of a multi-analyte screening algorithm for placental development in the first trimester.

Analyte relationships

	ANG-2	PIGF	PP-13	PTX-3
Age / race	−/−	−/−	−/−	−/−
Parity	−	−	−	−
BMI	***	−	**	−
MAP	**	*	−	−
Caffeine	−	−	−	−
Uterine Doppler	−	*	−	−
Umbilical Doppler	−	*	−	−

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10 HYPERTENSIVE DISORDERS IN PREGNANCY, RECURRENCE IN A SECOND PREGNANCY, AND SUBSEQUENT CARDIOVASCULAR EVENTS.

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OBJECTIVE: Hypertensive pregnancy disorders have been associated with subsequent death and ischemic heart disease. Minimal data exists concerning the relationship between hypertensive pregnancy disorders, other subsequent cardiovascular events or type 2 diabetes mellitus.

STUDY DESIGN: We conducted a registry based retrospective cohort study of women giving birth in Denmark from 1978 to 2007. A cohort of 782,287 women having a first singleton delivery was followed for 14.6 years yielding 11,600,945 person-years; and a cohort of 536,419 women having two first deliveries of singletons was followed for 12.9 years yielding 6,990,836 person-years.The primary exposure was hypertensive disorders in pregnancy stratified into gestational hypertension, mild and severe preeclampsia. Endpoints were subsequent hypertension, ischemic heart disease, congestive heart failure, thromboembolic event, stroke, and type 2 diabetes mellitus. We used time-to-first event using the Cox proportional hazard model to calculate the associations.

RESULTS: The adjusted hazard ratio of subsequent hypertension was 5.12 (4.73-5.54) after gestational hypertension, 3.52 (3.34-3.71) for mild preeclampsia, and 6.36 (5.72-7.09) for severe preeclampsia. The adjusted hazard ratio of subsequent type 2 diabetes mellitus was 3.5 ($p<0.001$) after any type of hypertensive disorder in pregnancy. The adjusted hazard ratio of subsequent thromboembolism after gestational hypertension was 1.02 (0.73-1.41), and 1.48 (1.28-1.71) and 1.59 (1.22-2.08) after mild and severe preeclampsia, respectively. Women having at least two pregnancies both complicated by preeclampsia had an adjusted hazard ratio of subsequent hypertension of 5.92 (5.32-6.59) compared to 2.69 (2.50-2.89) for women having preeclampsia in their first pregnancy only, and 4.14 (3.79-4.52) in their second pregnancy only.

CONCLUSION: Hypertensive disorders in pregnancy are strongly associated with subsequent hypertension and type 2 diabetes mellitus. The severity and recurrence of these pregnancy complications increase the risk of subsequent cardiovascular events.

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11 MATERNAL SERUM BIOMARKERS OF GESTATIONAL HYPERTENSION DISTINCT FROM PREECLAMPSIA

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OBJECTIVE: To characterize the maternal serum proteome profile in gestational hypertension (GH).

STUDY DESIGN: . A total of 130 women from a prospective observational cohort were included in this study. Maternal serum samples were collected between 21 and 37 gestational weeks. GH and preeclampsia (PE) were classified by Working Group criteria (Am J Obstet Gynecol 2000;183). Maternal serum proteome analysis was performed using multidimensional liquid chromatography tandem mass spectrometry (2D LC-MS/MS) and label-free quantification (spectral counting). Pairwise comparison was performed using $\chi 2$ goodness-of-fit tests and adjusted for multiple comparisons via the false-discovery rate (FDR) method. Immunoassays were used for accurate quantification and evaluated using the Receiver Operating Characteristic (ROC) curves and logistic regression analysis.

RESULTS: 14 women developed GH at a mean of 32 weeks gestation, 29 developed mild PE (mean 35 weeks), 29 developed severe PE (mean 31 weeks), and 58 remained normotensive and delivered at term. 2D-LC-MS-MS analysis of maternal sera identified 480 unique proteins for label-free quantification. Cluster analysis showed a unique cluster of proteins differentially expressed in GH distinct from mild and severe PE. Label-free quantification identified 36 differentially expressed ($p<0.05$) proteins between patients with GH compared to PE. These included cytoskelatal proteins (talin, filamin A, tropomyosin alpha, actin aortic smooth muscle); placental proteins (PAPPA-2, HCG); and matrix proteins. Analysis of 17 potential biomarkers with specific immunoassays showed good discriminating capability between GH and PE (AUROC's 0.73 to 0.82). Multi-analyte analysis showed further increased the discriminant ability (AUROC>0.88).

CONCLUSION: Systematic and comprehensive maternal serum proteome analyses identified a multi-analyte panel of serum biomarkers for GH. Reliable diagnosis of GH that could distinguish from PE could facilitate early and specific intervention strategies.

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12 EFFECT OF A SHORT-COURSE OF RECOMBINANT HUMAN VASCULAR ENDOTHELIAL GROWTH FACTOR ON VASCULAR DYSFUNCTION IN A MOUSE MODEL OF PREECLAMPSIA INDUCED BY SFLT-1 OVER-EXPRESSION.

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OBJECTIVE: Inhibition of angiogenesis, endothelial dysfunction and nitric oxide deficiency have been implicated in the pathogenesis of preeclampsia. Overexpression of sFlt-1 in pregnant rodents induces a preeclampsia-like condition characterized by abnormal vascular function. Our objective was to test the hypothesis that vascular endothelial growth factor (VEGF121; an angiogenic factor and ligand for Flt-1) reverses the vascular dysfunction in pregnant mice over-expressing sFlt-1.

STUDY DESIGN: CD-1 mice at day 8 of gestation were injected with adenovirus carrying sFlt-1 (10^9 PFU). At day 10 of gestation, the animals were randomly allocated to injections of VEGF121 (200μg/kg) or saline 100μl SC daily for 5 days (n=4/group). At day 18 of gestation, the mice were sacrificed and 2 mm segments of carotid artery were mounted in a wire myograph for isometric tension recording. Contractile response to KCl (10^{-5} M) and concentration-response curves to the endothelium-dependent vasodilator acetylcholine (Ach, 10^{-10}-10^{-5} M), the endothelium-independent vasodilator sodium nitroprusside (SNP, 10^{-10}-10^{-5} M), phenylephrine (PE, 10^{-10}-10^{-5} M), and thromboxane A2 (TxA2, 10^{-10}-10^{-6} M) were obtained. ANOVA was used for statistical analysis (significance: $p<0.05$).

RESULTS: Responses to KCl were not significantly different between the VEGF and saline groups. The maximal response to PE in the VEGF group was significantly higher compared with the saline group (150.2±33.5 and 76.40±42.4). This difference was abolished in the presence of the nitric oxide synthase inhibitor L-NAME. There was an increase in the relaxant response to Ach in the saline group compared with the VEGF group. The response to SNP was higher, but not significantly, in the VEGF group. No differences were noted in the TXA2 responses.

CONCLUSION: A short course of VEGF does not reverse, and may actually worsen, the vascular dysfunction seen in this animal model of preeclampsia. The paradoxical response may be related to mechanisms induced by sFlt-1 that are independent of VEGF inhibition. Longer courses need to be evaluated.

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