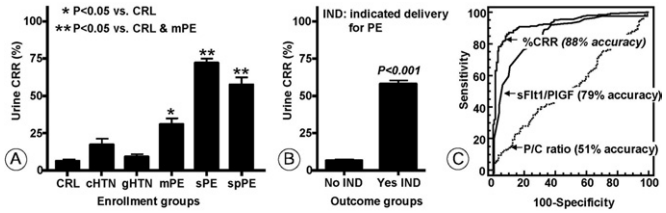
INDs occurred preterm and 51% (107/211) <34w GA. CRR was elevated in mPE and further increased in sPE and spPE independent of GA (A). Women requiring IND had elevated CRR at enrollment (B, P<0.001). Among women followed longitudinally, 11% (4/35) had preterm IND. In this group, CRRs was increased 14±4w prior to clinically manifest PE. CRR had higher accuracy in predicting IND compared to sFlt1/PlGF (P=0.014) and P/C (P<0.001) (C).

CONCLUSION: Assessment of global protein misfolding load by CRR is a simple diagnostic test for PE and for prediction of IND, an important contributor to preterm birth.



0002-9378/$ – see front matter • doi:10.1016/j.ajog.2009.10.052

21 Placental ischemia triggers immune activation as leukocyte overproduction of SFLT-1: a step in the pathogenesis of preeclampsia?

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OBJECTIVE: Plasma, amniotic fluid, and placental soluble fms-like tyrosine kinase (sFlt-1) mRNA is increased in patients with preeclampsia. Leukocytosis frequently accompanies the onset of HELLP syndrome. Investigators, including the ones at our lab, have shown placental ischemia (PI), circulating TNF alpha and agonistic autoantibodies to the angiotensin II type I receptor to be important stimuli for sFlt-1 production during pregnancy. These studies suggest that immune activation in response to PI may play a role in sFlt-1 production. The objective of this study was to determine if leukocytes stimulated in rats with PI are a source of circulating sFlt-1.

STUDY DESIGN: Sprague-Dawley rats were anesthetized on day 14 of pregnancy and underwent either examination under anesthesia (NP) or reduced uterine perfusion pressure (RUPP) in which the lower abdominal aorta above the iliac bifurcation (0.203mm ID clip) and both ovarian arteries (0.100mm ID clip) were isolated and chronically constricted. Rats were instrumented with a carotid catheter for arterial pressure measurement (MAP) on day 19. Plasma was collected in EDTA and leukocytes were isolated utilizing Lymphoprep centrifugation technique. Leukocytes were cultured overnight in RPMI media containing, 1.022 ng/ml IL-2 and 4 ng/ml IL-12 at 5% CO2 and 37°C. Cell culture media was removed and utilized in ELISA to determine sFlt-1.

RESULTS: MAP increased from 102 +/− 1 mmHg in NP rats to 127 +/− 2 mmHg in response to PI in RUPP rats. Circulating sFlt-1 was 963 pg/ml in NP rats vs. 1493 pg/ml in RUPP rats. In addition, sFlt-1 from NP PBL culture was 30+/−8 pg/ml. SFlt-1 from RUPP PBL culture increased significantly to 88+/−20 pg/ml (P <0.01).

CONCLUSION: The mechanisms whereby sFlt-1 over expression occurs during preeclampsia are not well defined. This study demonstrates that immune cells are activated during hypertension in response to PI to be a source for excess sFlt-1.

0002-9378/$ – see front matter • doi:10.1016/j.ajog.2009.10.053

22 Maternal, paternal and fetal single nucleotide polymorphisms in vascular endothelial growth factor family genes associate with pregnancy complications

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OBJECTIVE: Gestational hypertension (GHT), preeclampsia (PE) and pregnancies complicated by small for gestational age babies (SGA) contribute to maternal and neonatal morbidity and mortality. Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) are angiogenic factors which act via Flt-1 (fms-like tyrosine kinase 1) and KDR (kinase insert domain receptor) receptors. Reduced maternal plasma VEGF and PlGF and elevated sFlt-1 are implicated in PE and SGA. We hypothesised that polymorphisms in VEGF (C2578A), PlGF (C642A), KDR (T604C) and Flt-1 (C677T) genes associate with pregnancy complications.

STUDY DESIGN: 1169 nulliparous pregnant women and their partners were recruited prospectively for the Adelaide SCOPE study. GHT, PE and SGA were classified using strict guidelines. Uncomplicated pregnancies served as controls. Peripheral blood from couples and cord blood from babies were collected. DNA extraction and genotyping were performed using the Sequenom MassARRAY system. Genotypes for caucasian GHT (n=74), PE (n=71) and SGA (n=101) were compared with controls (n=408) and analysed using ANOVA and Chi Square.

RESULTS: Neonatal VEGFC2578A associate with PE (p=0.01, OR=2.3, 95%CI=1.2-4.4). Maternal and neonatal PlGFC642A associate with GHT (p=0.01, OR=1.14, 95%CI=1.2-7.9; p=0.027, OR=4.65, 95%CI=1.1-19.8). Paternal and neonatal KDRT604C associate with PE (p=0.04, OR=1.9, 95%CI=1.0-3.5; p=0.03, OR=2.2, 95%CI=1.1-4.4). Paternal and neonatal KDRT604C associate with SGA (p=0.004, OR=2.1, 95%CI=1.3-3.5; p=0.009, OR=2.2, 95% CI=1.2-3.9). Neonatal KDRT604C CC associate with 9.9 lower customised birthweight centile (p=0.039), 198g lower birthweight (p=0.013) and 61g lower placental weight (p=0.007) compared to TT. Paternal KDRT604C CC associate with 10.5 lower customised birthweight centile compared to CT (p=0.004).

CONCLUSION: Our results suggest that maternal and importantly paternal SNPs in VEGF family genes act through the placenta to confer risk for pregnancy complications. Ongoing research will determine the role of these polymorphisms in placental function.

0002-9378/$ – see front matter • doi:10.1016/j.ajog.2009.10.054

23 Effect of continuous delivery of recombinant vascular endothelial growth factor on vascular reactivity in a SFLT-1 induced animal model of preeclampsia

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OBJECTIVE: Maternal vascular dysfunction has been implicated in the pathogenesis of preeclampsia and confirmed in an animal model of preeclampsia induced by over-expression sFlt-1. Our objective was to evaluate the effect of exogenous vascular endothelial growth factor (VEGF) on in-vitro vascular function in the sFlt-1 mouse model of preeclampsia.

STUDY DESIGN: At day 8 of gestation, CD-1 pregnant mice were randomly allocated to continuous 0.5 μl/hr osmotic infusion of either VEGF-121 (400 μg/kg/day) or phosphate buffered-saline (solvent control) for 10 days. At day 9, animals were injected with adenovirus carrying sFlt-1 (10^9 PFU). At day 18 of gestation, the mice were sac-