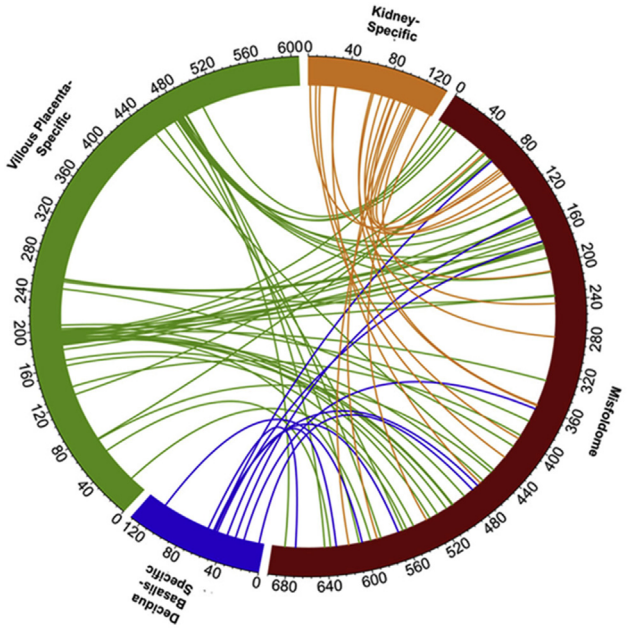
the potential contribution of kidney and placental transcripts to the urine misfoldome in PE.

STUDY DESIGN: Urine from 92 pregnant women was classified by strict clinical criteria in 6 groups: pregnant controls (CRL, n=11, GA: 30±5 wks), mild PE (mPE, n=15, GA: 33±4 wks), severe PE (sPE, n=21, GA: 32±4 wks), superimposed PE (spPE, n=16, GA: 32±6 wks), atypical PE (HELLP±IUGR, n=16, GA: 30±5 wks), and non-PE isolated proteinuria (n=13, GA: 28±6 wks). Misfoldome proteins were enriched by Congo Red precipitation and subjected to UPLC/MS/MS. Deep RNA sequencing (RNA-seq) was performed on decidua basalis (n=5) and villous trophoblast (n=5) of women with preterm severe PE (GA: 32±1 wks). These reads, together with RNA-Seq data from the Illumina Human BodyMap 2.0 database (n=16, adult tissues including kidney), were used to intersect specific transcripts that may contribute to aberrant proteinuria in PE.

RESULTS: 646 unique proteins IDs comprised the urinary misfoldome of PE women. Our intersection analysis showed a potential contribution of villous trophoblast, decidua and kidney to the misfoldome (Figure). Villous trophoblast was a larger contributor than either kidney or decidua (Table). Kidney-specific transcripts such as solute carrier family 22 (SLC22A12, a urate transporter), SMIM24 (an uncharacterized small integral membrane protein), MMP7 (matrilysin), and CALB1 (calbindin 1, a protein linked to Huntington disease) mapped to distinct PE subphenotypes.

CONCLUSION: The urinary misfoldome harbors a considerable number of peptides of placental and kidney origin which may interact to play key pathogenic roles in various PE subphenotypes.



Circos plot showing shared IDs among the urine misfoldome (red) and transcripts specific to the villous trophoblast (green), kidney (orange) and decidua basalis (blue). The size of each sector is proportional to the number of unique IDs in each group, and connecting chords represent shared IDs.

The Number of Villous Trophoblast, Decidua, and Kidney Transcripts Contributing to the Misfoldome

Transcripts Mapped to Misfoldome per Condition	sPE, Villous Trophoblast-Specific	sPE, Decidua-Specific	Kidney-Specific
CRL (n=230)	23	4	3
Non-PE Proteinuria (n=265)	31	2	4
mPE (n=368)	30	5	9
sPE (n=437)	37	4	8
Atypical PE (n=332)	21	3	5
spPE (n=351)	36	5	7

183 Interleukin 1 beta is increased in the hippocampus and posterior cortex of rats with hypertension and systemic inflammation during pregnancy

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OBJECTIVE: HELLP syndrome is a severe form of preeclampsia. We have previously shown that both women and animals with HELLP have an increase in T cells, inflammatory cytokines and blood brain barrier (BBB) permeability. Our objective was to determine if rats with HELLP have evidence of BBB permeability and increase in inflammatory cytokines within the brain.

STUDY DESIGN: On gestational day (GD) 12 we infused sEndoglin and sFlt-1 (7 and 4.7ug/kg/day respectively) via a mini-osmotic pump into timed-pregnant rats. Rats not infused served as normal pregnant (NP) controls. On GD19, MAP was measured via carotid arterial catheters placed on GD18, tissues collected, animals euthanized. The brain was weighed, dissected and frozen until assay prep. The cerebellum, hippocampus, frontal and posterior cortex were defrosted on ice. Tissue was homogenized on ice in ice-cold Tris buffer (pH7.4) with protease inhibitor cocktail. Homogenates were centrifuged and supernatants aliquoted. Samples were run using a Milliplex Kit (EMD Millipore) assaying for these cytokines: IL-4, IL-1β, IL-6, IL-10, IL-17A, and VEGFA. All samples were normalized to total protein using the bicinchoninic acid assay. Data was analyzed with a repeated measures two way ANOVA with a Bonferroni post-hoc analysis if applicable. $P<0.05$.

RESULTS: MAP was significantly increased in HELLP rats compared to NP rats ($p=0.04$; n=4-5/group) on GD19. Infusion of Texas Red dextran on GD19 led to higher dye leakage in the posterior cortex and brainstem of HELLP rats compared to NP rats when viewed by in vivo imaging (IVIS Lumina), indicative of BBB permeability. IL-1β was significantly increased in the posterior cortex ($p=0.03$) and hippocampus ($p=0.01$) of HELLP rats compared to NP rats. There were no significant differences in the frontal cortex ($p=0.996$) between the groups. In the cerebellum IL-1β was significantly decreased ($p=0.002$) compared to NP rats as was IL-6 ($p=0.03$). There were no significant differences between HELLP and NP rats in any other cytokines measured.

CONCLUSION: These findings suggest that levels of inflammation in the posterior and hippocampal regions of HELLP rats may indicate increased anxiety or cognitive disorders such as changes in learning and memory or reflective of the posterior reversible encephalopathy syndrome.

184 Pre-eclampsia, diabetes, and the placenta: a study in differential gene expression & molecular clues to disease states

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OBJECTIVE: While the exact etiology of pre-eclampsia remains a mystery, the role of the placenta in the pathophysiology of pre-eclampsia continues to be implicated, making the placenta a prime

candidate for examining genetic perturbations in gravidae with pre-eclampsia and commonly found co-morbidities such as diabetes.

We previously investigated global placental gene expression among diabetic gravidae, by applying whole transcriptome RNA sequencing (RNA-Seq) and robust computational analysis and found novel changes in placental gene expression by virtue of maternal diabetic status. In this current study we examined a clinically relevant cohort of both diabetic and non diabetic gravidae with the aim of determining placental gene expression changes specific for frequently co-morbid, hypertensive disorders of pregnancies as compared to controls.

STUDY DESIGN: Whole transcriptome sequencing was undertaken with extensively clinically phenotyped, population-based subject placental samples (n=29) on the HiSeq (Illumina), rendering over 150 million reads/sample. RNA Seq computational analysis was used to identify significant placental gene expression differences among our cohort. Two independent, computational platforms (edgeR and DESeq2) were used to verify differential gene expression.

RESULTS: Significant placental gene expression differences were noted in the gravidae with pre-eclampsia as compared to controls (FDR <0.05). Additionally, significant differential gene expression was noted in gravidae with diabetes (both GDM and Type II) and pre-eclampsia when compared to those that had neither, after controlling for subjects with only diabetes or pre-eclampsia (FDR<0.05). Summary data are projected as a heat map (Figure) where values are log2 transformed read counts that have been quantile normalized. Subsequent annotation following control for multiple comparisons revealed significant differences in 782 genes mapping to multiple pathways (p<10-6).

CONCLUSION: Novel placental gene expression differences were seen when stratified by pre-eclampsia and diabetes status. This work in a large population-based cohort further emphasizes the synergistic nature of these conditions, and reveals underlying placental gene pathways which may drive maternal comorbidity.

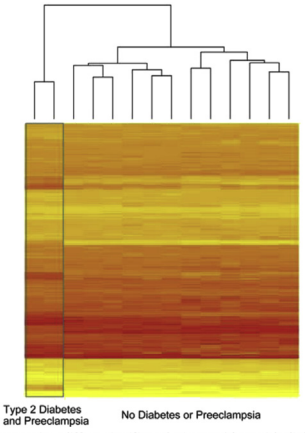

Figure 1. Placental gene expression differs significantly in gravidae with diabetes and pre-eclampsia as compared to controls. Significant differences in expression were noted in 782 genes (FDR<0.05) when comparing gravidae with both diabetes and pre-eclampsia to those without, after controlling for individuals with only diabetes or pre-eclampsia.

185 Serelaxin improves endothelial dysfunction and uterine artery resistance in response to placental ischemia during pregnancy

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OBJECTIVE: Examine the effect of Serelaxin in improving endothelial function and reducing uterine artery resistance index in response to placental ischemia.

STUDY DESIGN: On day 14 of gestation, Sprague Dawley rats entered the RUPP, RUPP+Relaxin or Normal pregnant (NP) control groups. Pregnant rats entering the RUPP and RUPP+Relaxin groups underwent the application of a constrictive silver clip (0.203 mm) to the aorta superior to the iliac bifurcation and ovarian clips (0.100 mm) bilateral uterine arcades at the ovarian ends. Those in the RUPP+Relaxin group received a Serelaxin mini-osmotic pump. Carotid catheters were inserted on GD18. MAP, blood and tissues were collected on GD19.

RESULTS: MAP in normal pregnant (NP) rats (n=5) was 106+5, 128+3 in RUPP rats (n=10) and 110+3 mmHg in RUPP+Serelaxin (n=10), p<0.05. UARI was 0.66+0.01 in RUPP rats (n=6), but was improved to 0.59+0.02 in RUPP+Serelaxin (n=4), p<0.05. Circulating nitrate-nitrite, measured by ELISA, was 16.0+2.4 in RUPP rats (n=9), which increased to 25.4+2.5 μM in RUPP+Serelaxin (n=6), p<0.05. We established that PPET-1 expression increases in RUPP aortas, kidneys and placentas by 20, 3 and 22 fold respectively as compare to NP. Serelaxin reduced PPET-1 expression in aorta, kidneys and placentas by 5, 2 and 3.72 fold as compare to RUPP.

CONCLUSION: Serelaxin improves MAP, UARI and nitric oxide bioavailability, and decreases the expression of PPET-1 in placental, renal cortex and aortic tissue. These data suggest an important role for relaxin in maintaining normal blood pressure and vascular compliance during pregnancy which would be helpful to maintain maternal health and prolong pregnancy in the face of placental ischemia.

186 Sequential angiogenic factor estimation, adverse perinatal outcomes and pregnancy duration among patients admitted for evaluation of preeclampsia

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OBJECTIVE: Angiogenic factors correlate with adverse outcomes when measured in women with suspected preeclampsia in third trimester. No data exists evaluating their sequential levels among admitted patients.

STUDY DESIGN: This was an observational cohort study among women with singleton pregnancies admitted for evaluation of pre-eclampsia <37 weeks gestation in a tertiary hospital in Boston. Plasma samples were collected upon admission and every day for the first three days and then weekly till delivery. Maternal demographics, hospital course, mode of delivery, diagnosis of hypertensive disorder and adverse maternal and neonatal outcomes were collected from patient's charts. Angiogenic factors (sFlt1 and PlGF) were measured on automated platform.

RESULTS: During the study period 100 women were enrolled and 43 had adverse outcomes. Women with adverse outcomes had higher sFlt1 and sFlt1/PlGF ratio on admission and continued to have an increase in levels throughout hospital course. The median (25th-75th) sFlt1/PlGF ratio among patients with adverse outcomes was 205.9 (72.5, 453.1) versus 47.5 (9.7, 87.0) among women without adverse outcomes (P<0.001). The median (25th-75th) absolute change per day in sFlt1 levels (pg/ml) was 491.0 (120.3, 1587.2) among women with adverse outcomes versus 81.3 (-177.9, 449.0) among women without adverse outcomes (P=0.01). Similarly the absolute change per day for sFlt1/PlGF ratio was 15.1 (1.8, 58.1) versus 2.7 (-0.6, 8,3) among the two groups (P=0.004). The mean