

**STUDY DESIGN:** Searches were conducted in PubMed, Medline, Embase, and Cochrane library, using the following text words: preeclampsia, low-dose aspirin, acetylsalicyl acid, vitamins C/E, antioxidants, antiplatelets. Randomized trials that compared the effectiveness of LDA or VCE with placebo in women at high or low risk for PE were included if PE was defined according to the guidelines of the International Society for the Study of Hypertension in Pregnancy. Study selection and data extraction were performed by the two Authors independently by following QUORUM guidelines. Discordance was resolved by consensus. Articles were stratified according to the treatment performed to prevent PE and successively for the presence or absence of risk factors. Outcomes of interest were: incidence of PE, any hypertensive disorder, preterm delivery, small for gestational age, perinatal death, and maternal complications that could be attributed to adverse effects of LDA and VCE. Inter-studies heterogeneity was tested for all analyses. Pooled OR with 95% CI were computed at a significant level of  $P < 0.05$ .

**RESULTS:** Fifteen studies were reviewed from January 1988 to April 2008. LDA did not decrease the incidence of PE in high-risk (396/5025-8% vs placebo: 464/5027-9%;  $P=0,05$ ) and low-risk (137/4939-3% vs placebo: 166/4962-3%;  $P=0,10$ ) women. Similarly, VCE did not reduce the incidence of PE in high-risk (VCE: 250/1744-14% vs placebo: 275/1741-16%;  $P=0,24$ ) and low-risk (VCE: 56/935-6% vs placebo 47/942-5%;  $P=0,57$ ) women. In high-risk women, other hypertensive disorders were more frequent in women receiving VCE (121/1692-7%) than placebo (79/1693-5%;  $P=0,002$ ; OR:1,59; 95%CI: 1,18-2,13). Perinatal outcomes were not improved by LDA or VCE.

**CONCLUSION:** There is no evidence to support the administration of LDA or VCE to prevent PE in women at high or low risk.

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#### 741 Possible involvement of placental IL-1 system in preeclampsia

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**OBJECTIVE:** To evaluate the levels of IL-1a, IL-1b and their natural inhibitor IL-1 receptor antagonist (IL-1Ra) in different placental compartments of normotensive and preeclamptic placentas.

**STUDY DESIGN:** Placental tissue samples (amnion, chorion, placental villous and decidua) were collected from term (37-40 W) normotensive ( $n=18$ ), term preeclamptic ( $n=12$ ) and preterm preeclamptic ( $n=6$ ) placentas, immediately after caesarean delivery. Tissue samples were homogenized and examined for IL-1a, IL-1b and IL-1Ra levels by ELISA. Statistical significance was determined using 2-way analysis of variance (ANOVA).

**RESULTS:** IL-1Ra was mainly produced by the amnion of normotensive ( $p < 0.01$ ) and preeclamptic ( $p < 0.05$ ) placentas as compared to other placental compartments, while there were no significant differences in IL-1a and IL-1b production between different placental compartments. No significant differences were detected in IL-1a, IL-1b and IL-1Ra levels in preeclamptic as compared to normotensive placentas, although a tendency of higher IL-1b levels in all preeclamptic placental compartments compared to normotensive placentas was observed. However, significantly higher IL-1:IL-1Ra ratio was detected in the chorion compartment of preeclamptic placentas, as compared to normotensive placentas ( $p < 0.05$ ). There were no significant differences in IL-1a, IL-1b or IL-1Ra levels in preeclamptic placentas from term deliveries, as compared to preeclamptic placentas from preterm deliveries.

**CONCLUSION:** The human placenta may keep decreased IL-1: IL-1Ra ratio in the fetal membranes by producing high levels of IL-1Ra. IL-1: IL-1Ra ratio in the fetal membranes seems to be increased in preeclampsia, suggesting a role for the IL-1 system in the pathogenesis of PE.

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#### 742 Magnesium sulfate does not affect prostaglandin E2 secretion by normotensive nor preeclamptic placenta

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**OBJECTIVE:** To examine the effect of magnesium sulfate (MgSO<sub>4</sub>) on prostaglandin E2 (PGE<sub>2</sub>) secretion by normotensive and preeclamptic placentas.

**STUDY DESIGN:** Cotyledons of term normotensive and preeclamptic placentas were dually perfused for 6 hours (6h), with MgSO<sub>4</sub> (6-7 mg %) in the maternal reservoir [normotensive ( $n=3$ ); preeclamptic ( $n=5$ )] and with control medium (without MgSO<sub>4</sub>) [normotensive ( $n=3$ ); preeclamptic ( $n=5$ )]. Perfusate samples from the maternal and the fetal circulations were collected every 60 min for 6h of perfusion, and examined for PGE<sub>2</sub> levels by radio-immuno assay (RIA). RIA results were normalized for gram of perfused cotyledon. Statistical significance was determined using 2-way analysis of variance (ANOVA).

**RESULTS:** A prominent tendency toward increased PGE<sub>2</sub> levels in the fetal and the maternal circulations of preeclamptic placentas as compared to normotensive placentas was observed reaching near significant differences between the two placental groups. Moreover, PGE<sub>2</sub> levels in the fetal circulations of normotensive and preeclamptic placentas were significantly higher compared to the maternal circulations, reaching peak values after 60 min of perfusion [(normotensive;  $0.019 \pm 0.011$  ng/mL/gr cotyledon vs.  $0.002 \pm 0.004$  ng/mL/gr cotyledon;  $p < 0.05$ ); (preeclamptic;  $0.041 \pm 0.027$  ng/mL/gr cotyledon vs  $0.008 \pm 0.008$  ng/mL/gr cotyledon;  $p < 0.05$ )]. Perfusion of normotensive and preeclamptic placentas with MgSO<sub>4</sub> did not affect PGE<sub>2</sub> secretion levels into the fetal or the maternal circulations.

**CONCLUSION:** The placenta may play an important role in maintaining high levels of PGE<sub>2</sub> in the fetal circulation and low PGE<sub>2</sub> levels in the maternal circulation during normal or preeclamptic pregnancies. Placental PGE<sub>2</sub> secretion seems not to be altered during preeclampsia. MgSO<sub>4</sub> does not affect PGE<sub>2</sub> secretion by normotensive nor preeclamptic placenta.

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#### 743 Genetic variation in G-protein coupled receptor kinase-5 and preeclampsia

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**OBJECTIVE:** G-protein coupled receptor kinases (GRK) tightly control receptor binding which regulates blood vessel radius and pressure. GRK gene variation has been associated with hypertension and cardiovascular disease in non-pregnant adults. We sought to examine the contribution of GRK-5 genetic variation to hypertensive disorders in pregnancy.

**STUDY DESIGN:** Healthy Pregnancy, Healthy Baby is a prospective cohort of pregnant women aimed at identifying genetic, social, and environmental contributors to disparities in pregnancy outcomes. English-literate women >18 years with a normal singleton pregnancy

<28 weeks, residing within Durham County, NC were enrolled. Data were available for 513 women (77% non-Hispanic black race). Hypertensive disorders included chronic hypertension (CHTN=BP>140/90 before 20 wks), preeclampsia (BP>140/90 and proteinuria), and CHTN + superimposed preeclampsia (CHTN with new onset or worsening proteinuria). Haplotype tagging single nucleotide polymorphisms (SNPs) were genotyped for GRK-5 via Taqman assays. Logistic regression was used to examine the relationship between maternal genotype and each hypertensive disorder, adjusting for race, age, education, insurance, tobacco use, and pre-pregnancy BMI. CHTN was included as a covariate in the model for preeclampsia.

**RESULTS:** 94 participants (18%) were diagnosed with preeclampsia. Of the 17 SNPs examined, 2 were associated with preeclampsia. For rs4752274 (global p=0.049), GG genotype was associated with an increased risk for preeclampsia relative to TT genotype (OR 2.48, [95%CI 1.20, 5.12], p=0.01). For rs506657 (global p=0.039), both the CC and CT genotypes had an increased risk for preeclampsia relative to TT genotype (CC: OR 2.99 [95%CI 1.16, 7.7], p=0.02 and CT: OR 3.38 [95%CI 1.32, 8.66], p=0.01). There was no association between genotype and CHTN or CHTN+preeclampsia.

**CONCLUSION:** The GRK-5 gene may play a role in the development of preeclampsia. Future analyses will examine the effects of GRK-5 on blood pressure regulation and potential pharmacogenomic interactions during pregnancy.

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**744 Umbilical cord levels of insulin like growth factor-1 and insulin like growth factor binding protein-3 in pregnancies complicated by preeclampsia**

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**OBJECTIVE:** To compare umbilical cord levels of insulin like growth factor-1 (IGF-1) and insulin like growth factor binding protein-3 (IGFBP-3) between gravid women at term with and without preeclampsia.

**STUDY DESIGN:** A cross sectional study of 84 healthy and 39 women with term preeclampsia and their infants was performed. Maternal serum was collected upon admission for delivery and infant cord blood was collected at delivery. Preeclampsia was defined by ACOG criteria. Maternal and umbilical cord serum IGF-1 and IGFBP-3 levels were measured using immunoradiometric assays. Statistical analysis included student t-test, chi square, Mann Whitney U, and linear regression.

**RESULTS:** Umbilical cord levels of insulin like growth factor-1 were significantly lower in the preeclamptic group than in the control group (33.9 ng/mL [IQR 24.3 – 47.5] vs 41.9 ng/mL [IQR 27.3 – 60.9], p < 0.02). There was no difference in umbilical cord insulin like growth factor binding protein- 3 levels between the preeclamptic and control group (1404.3 ng/mL [IQR 1010.3-1604.6] vs 1254.4 ng/mL [IQR 957-1554.1], p = 0.39). In multivariable linear regression body mass index (p =0.009) and preeclampsia (p=0.004) were independently associated with cord IGF-1 levels.

**CONCLUSION:** Term infants born to mothers with preeclampsia have lower cord levels of IGF-1 than infants born to term healthy women. This reduction in cord IGF-1 levels may be due to the pathophysiology of preeclampsia or as a consequence of the condition.

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**745 Screening for preeclampsia using first trimester serum markers in nulliparous women**

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**OBJECTIVE:** To evaluate the screening efficacy of different maternal serum biomarkers during the first trimester for the prediction of pregnancy hypertensive disorders. To establish a prediction model based on their combination.

**STUDY DESIGN:** In this prospective cohort study, women were recruited at the time of first trimester screening for Down syndrome and followed until delivery. Serum samples for measurement of placental biomarkers (PAPP-A, Inhibin A, PP13, ADAM12, free beta-HCG, PIGF) were collected at 11-14 weeks in all women and assayed (AutoDelfia, PerkinElmer, Finland). PIGF was measured only in the second half of the cohort. Results were expressed as multiples of the median (MoM) adjusted on maternal characteristics, including body mass index (BMI), ethnicity, smoking and gestational age at sampling. ROC curves were used to analyze the predictive value of each parameters. Different models combining biomarkers were obtained by logistic regression.

**RESULTS:** Among 893 nulliparous women, 20 developed gestational hypertension (2.2%) and 40 developed preeclampsia (4.5%), including 9 early-onset preeclampsia with diagnosis before 34 weeks (1.0%) and 16 severe preeclampsia (1.8%). Table 1 shows median MoMs of markers. PP-13 and ADAM12 were strongly correlated with BMI (r= -0.27 and r= -0.26, p<0.001), but did not predict preeclampsia after adjustment. Using PAPP-A, Inhibin A and PIGF, a combined screening model could detect 75% of early-onset preeclampsia and 23% of total preeclampsia with a 4% false-positive rate.

**CONCLUSION:** A combination of first trimester maternal serum biomarkers (PAPP-A, Inhibin A, PIGF) could be an effective screening tool for early-onset preeclampsia. However, we did not confirm the predictive value of PP13 after adjustment for BMI.

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**Table 1. Median of first trimester markers in cases (MoM) - Reference=1 MoM in controls - PE=preeclampsia - GH=Gestational hypertension**

	PE	Early PE	GH
PAPP-A N=889	0.93	0.69	0.73
Inhibin A N=885	0.99	1.49	0.85
PP-13 N=890	1.01	1.04	0.90
PIGF N=531	0.76	0.73	1.05
ADAM12 N=888	0.98	1.02	1.05
hHCG N=889	0.80	0.77	1.04

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