CONCLUSION: Decreased first trimester levels of ADAM12s may be useful in early prediction of PIH. Decreased levels of PP13 were not significantly correlated with adverse pregnancy outcome. Combining ADAM12s and PP13 does not appear to improve screening performance.

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47 Associations with preeclampsia: lessons from the hyperglycemia and adverse pregnancy outcome (HAPO) study

Yariv Yogev[1], Rony Chen[1], Moshe Hod[1], Donald Coustan[2], Jeremy JN Oats[3], Boyd Metzger[4], Lynn Lowe[4], Alan R Dyer[4], Elisabeth Trimble[5], David Hadden[6], Bengt Persson[7], for the Hapo Study Cooperative Research Group[8]

[1]Rabin Medical Center Beilinson Campus, Tel Aviv University, Petah Tikvah, Israel, Perinatal Division and WHO Collaborating Center, Tel Aviv, Israel, [2]Warren Alpert Medical School of Brown University/ Women & Infants Hospital of RI, Obstetrics and Gynecology, Providence, Rhode Island, [3]Royal Women's Hospital, University of Melbourne, Victoria, Australia, [4]Northwestern University Feinberg School of Medicine, Chicago, Illinois, [5]Queens University Belfast, United Kingdom, [6]Royal Victoria Hospital Belfast, United Kingdom, [7]Karolinska Institute, Sweden, [8]Northwestern University, Illinois

OBJECTIVE: To examine associations of maternal glucose levels, BMI and fasting serum C-peptide with the risk of preeclampsia (PE), in the multicenter multinational HAPO Study.

STUDY DESIGN: Secondary analysis of double blinded prospective observational cohort study. Eligible pregnant women underwent a standard 75-g oral glucose tolerance test (OGTT) between 24 and 32 weeks gestation (mean 27.8 weeks). Preeclampsia includes PE, severe PE, eclampsia, and PE superimposed on chronic HTN. Women with gestational or chronic HTN were excluded. Associations between PE and maternal glucose, fasting serum C-peptide and BMI (measured at the OGTT) were assessed using multiple logistic regression analyses, with adjustment for potential confounders including field center, family history of hypertension and diabetes, maternal age, parity, height, gestational age at OGTT, smoking, alcohol use, and baby's sex.

RESULTS: 1) Overall, 21,364 of 23,316 blinded HAPO participants were eligible for analysis, of whom 1,116 (5.2%) developed PE. 2) Fully adjusted odds ratios (OR) for PE associated with a 1 SD higher fasting (6.9 mg/dl), 1-hour (30.9 mg/dl), and 2-hour plasma glucose (23.5 mg/dl) were 1.08 (95% CI 1.00-1.16)), 1.19 (95% CI 1.11-1.28), 1.21 (1.13-1.30), respectively). 3) For each 1 SD increment in maternal BMI (5.1 kg/m2) the adjusted OR was 1.60 (95% CI 1.50-1.71). 4)) For maternal fasting C-peptide the adjusted OR was 3.08 (95% CI 1.84-5.16) for the highest versus lowest category of C-peptide (>4.8 vs. <1.2 ug/L).

CONCLUSION: Our results indicate generally strong, continuous associations of maternal hyperinsulinemia, BMI and maternal glucose levels below those diagnostic of diabetes with preeclampsia. These findings support a possible role of insulin resistance in the pathogenesis of PE.

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48 Allelic variations in angiogenic pathway genes are associated with preeclampsia

Sindhu Srinivas[1], Alanna Morrison[2], Michal Elovitz[3]

[1]University of Pennsylvania, Maternal and Child Health Research Program; Dept of OBGYN; CRRWH, Philadelphia, Pennsylvania, [2]University of Texas Health Science Center at Houston, Houston, Texas, [3]University of Pennsylvania, Maternal and Child Health Research Program; Dept OBGYN; CRRWH, Philadelphia, Pennsylvania

OBJECTIVE: Alterations in the levels of angiogenic factors have been associated with the development of preeclampsia (PRE). Yet, there is a paucity of studies investigating allelic variants of genes controlling anti- and pro-angiogenic factors and PRE. This study investigates the association of allelic variations in genes in the angiogenic pathway and PRE.

STUDY DESIGN: Cases with PRE and term controls were prospectively collected between 2005-2007. Maternal DNA was extracted from blood. Clinical data was obtained by chart abstraction. The Illumina IBC array was used. 139 tagSNPs in 6 genes (VEGFA, VEGFB, VEGF C, FLT1, FLT4, ENG) were evaluated. SNPs deviating from HWE ($p<0.001$) in controls and those that were monomorphic in an ethnic group were not analyzed. MVLR was used to evaluate the association SNPs in angiogenic factor genes and PRE after controlling for maternal age. All models were evaluated in blacks and whites separately. Haplotype analyses were performed in genes with SNPs demonstrating a univariate association.

RESULTS: We analyzed data from 606 women. 489 black women (305 cases) and 117 white women (32 cases) were evaluated. In black women, the FLT1 rs12584067 (1.55 [1.01-2.36], $p=0.04$) SNP and rs7335588 SNP (0.62 [0.41-0.94], $p=0.02$) were significantly associated with PRE A VEGFC gene haplotype was associated with a reduced odds of PRE (0.58 [0.41-0.81], $p=0.002$). Additionally, 1 ENG, 3 FLT1, and 1 VEGFA SNPs were nominally associated with PRE. In white women, FLT1 rs722503 2.12 [1.07-4.19], $p=0.03$), FLT4 rs307826 (3.06 [1.18-7.91], $p=0.02$) and VEGFC rs7664413 (0.49 [0.24-1.01], $p=0.05$) SNPs were significantly associated with PRE.

CONCLUSION: Allelic variations in select genes in the angiogenic pathway are associated with PRE. These genetic variations may alter protein levels and thus, explain the abnormal serum levels of sFlt, ENG and PlGF seen in some women with PRE. Further research is needed to understand the association among serum levels of angiogenic factors, genetic polymorphisms and etiology of PRE in order to best predict clinical disease.

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49 Multiple ABC transporters of human placental brush border membranes contribute to the efflux of glyburide, rosiglitazone, and metformin

Sarah Hemauer[1], Svetlana Patrikeeva[1], Tatiana Nanovskaya[1], Gary DV Hankins[2], Mahmoud Ahmed[3]

[1]University of Texas Medical Branch at Galveston, Obstetrics and Gynecology, Galveston, Texas, [2]The University of Texas Medical Branch, Obstetrics and Gynecology, Galveston, Texas, [3]Society for Maternal-Fetal Medicine, Galveston, Texas

OBJECTIVE: The combined use of hypoglycemic drugs Glucovance (glyburide + metformin) and rosiglitazone has been evaluated in nonpregnant patients with type 2 diabetes mellitus. However, the role of the placenta in the biodisposition of a combination of oral hypoglycemic drugs during pregnancy remains unclear. Previous reports from our laboratory demonstrated that multiple drugs could compete for efflux by P-glycoprotein (P-gp). Therefore, co-administration of hypoglycemic drugs which are substrates of placental efflux transporters could introduce competition for a single efflux transporter thus increasing their transfer to the fetal circulation. The aim of this investigation was to identify the major human placental ABC transporters responsible for the efflux of glyburide, rosiglitazone, and metformin.

STUDY DESIGN: Inside-out brush border membrane vesicles (BBMVs) were prepared from trophoblast tissue of 60 term placentas obtained from healthy pregnancies. Chemical inhibitors selective for each of the ABC transporters P-gp, Breast Cancer Resistance Protein (BCRP), and Multidrug Resistance Protein 1 (MRP1) were used to inhibit the ATP-dependent uptake of [^{3}H]-glyburide, [^{3}H]-rosigitazone, or [^{14}C]-metformin by BBMVs.

RESULTS: The three transporters contributed to 78 ± 4 % of total glyburide efflux in placental BBMVs. The contributions of each transporter to the total efflux were MRP1 (43 ± 4%); BCRP (25 ± 5%); and P-gp (9 ± 5%). P-gp was responsible for 73 ± 1% of rosiglitazone efflux, with minimal contributions by BCRP and MRP1. ABC transporters extruded ~80% of metformin with 58 ± 20% achieved by P-gp and 25 ± 14% by BCRP.

CONCLUSION: The placental ABC transporters investigated each contribute to the efflux of glyburide, rosiglitazone, and metformin to a