DIABETES/HTN/MEDICAL-SURGICAL COMPLICATIONS

Abstracts 44 – 52

Moderators: Daniel O'Keeffe, MD; Haywood Brown, MD; Norman Gant, MD, Honorary Moderator

44 First trimester prenatal diagnosis of decreased fetal cardiac performance correlates with hyperglycemia in pregestational maternal diabetes

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OBJECTIVE: In vitro animal studies suggest that hyperglycemia impairs fetal cardiac function early in gestation. We aimed to study if evidence of first trimester myocardial dysfunction can be detected in fetuses of women with pregestational diabetes mellitus (DM).

STUDY DESIGN: Women with DM underwent fetal echocardiography at 11-14 weeks' gestational age (GA). Cardiac structure was studied in a segmental approach. Cardiac preload, diastolic function, global myocardial performance and placental afterload were studied by Doppler of the ductus venosus (DV), mitral and tricuspid E/A ratios, left and right ventricular Tei index and umbilial artery (UA) respectively. DM patients were matched for GA, UA and DV Doppler with normal controls.

RESULTS: After exclusion of structural cardiac anomalies 60 DM and 60 controls were studied at 12.6 weeks (11.1-13.6). UA and DV pulsatility indices (median 2.22 and 0.99) and nuchal translucency was (median 1.5 mm) were similar between cases and controls. DM patients had lower mitral E/A ratios than controls [0.55±0.08 vs 0.52±0.08, p=0.03). Left and right ventricular Tei indices were significantly higher in diabetics than in controls [0.51±0.08 vs 0.48±0.1; 0.51±0.08 vs 0.45±0.08, p<0.04 and <0.001]. This lower global myocardial performance was due to prolonged myocardial relaxation which was most marked in diabetics with a HbA1c >8. (0.001 for all parameters). No correlation between cardiac Doppler parameters and DV and UA indices were observed.

CONCLUSION: We demonstrate significant differences in first trimester diastolic myocardial perfomance in fetuses of diabetic mothers compared with non-diabetic controls. In addition, among the diabetics the decrease in myocardial performance was more marked with increasing hyperglycemia, and appears independent of preload and afterload. Our ability to document these changes this early in pregnancy opens potential new avenues to monitor and modify maternal glycemic control before cardiac remodeling such as myocardial hypertrophy develops.

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45 Effects of magnesium on central arterial compliance in preeclampsia

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OBJECTIVE: To investigate the effect of MgSO4 infusion on central arterial compliance, using noninvasive radial artery pulse wave forms by applanation tonometry in women diagnosed with preeclampsia (PRE).

STUDY DESIGN: This is a prospective observational study. Women diagnosed with PRE were recruited prior to receiving MgSO4. Measurements of the radial pulse waveform were obtained longitudinally. Using a validated internal transfer function, the aortic waveform was derived and the indices Augmentation Pressure (AP) and Augmentation Index corrected @75bpm (AIx@75) were calculated. The AP and AIx@75 are surrogate measures of arterial stiffness. We compared the time periods: prior to MgSO4 (t1), 1hr after MgSO4 bolus (t2), 4hrs after MgSO4 maintenance infusion (t3), 24hrs after delivery and MgSO4 completion (t4). An 80% power assuming an increase in compliance of 25%, =0.05, required 70 subjects. Statistical analysis was performed using differences of least squared means with Tukey Kramer adjustment. Institutional IRB approval was obtained.

RESULTS: Data was analyzed from seventy women. AP and AIx@75 at t2-t4 were significantly lower compared with t1, (pvalue =.008, <.001, and .002) and (pvalue =.039, <.001, and .005) respectively, with greatest decrease in arterial stiffness at t3- 4hrs after MgSO4 maintenance. AP and AIx@75 at t3 was significantly lower when compared with t2 (p-value<.001 and .001). AP at t3 was significantly lower compared with t4 (p=.018). No significant difference in AIx@75 was noted between t3 and t4.

CONCLUSION: In women with PRE, MgSO4 improved central arterial compliance. This effect was most exaggerated after 4hrs of infusion and remained 24hrs following MgSO4 completion following delivery. This suggests either a sustained vascular compliance effect from MgSO4 or resolution of the vasoconstrictive effect of preeclampsia. Further, MgSO4 may improve perfusion to end organs by decreasing arterial stiffness, this information could be used to direct future management, suggesting a benefit of its use beyond seizure prophylaxis.

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46 Maternal serum PP13 and ADAM12S as first trimester predictors of adverse pregnancy outcome

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OBJECTIVE: To investigate the value of first trimester maternal serum measurements of A Disintegrin And Metalloprotease 12-S (ADAM12s) and Placental Protein 13 (PP13) in the prediction of preeclampsia (PE), pregnancy induced hypertension (PIH) and intrauterine growth restriction (IUGR).

STUDY DESIGN: A retrospective case-control study of samples taken between 2004 – 2007 was conducted. Gestational age ranged from 9+0 to 13+6 weeks. All samples were collected as part of the national program for Down Syndrome Screening. All PE, PIH and IUGR cases were matched for exact gestational age and maternal age with three control cases. The serum concentration of ADAM12s and PP13 were analyzed 'blind' to outcome. Results were expressed in multiples of the median (MoM). MoM values were compared using Mann-Whitney U test and receiver-operator-characteristics (ROC) curves were used to asses screening performance.

RESULTS: 165 controls samples, 17 cases of PE, 30 cases of PIH and 8 cases of IUGR were identified. Median ADAM12s concentrations for controls versus cases were significantly reduced: 405 vs. 324 nG/L (MoM 1.00 vs. 0.80 ($p < 0.05$)). In PP13 no significant difference was found: 57.7 vs. 54.6 pG/L (MoM 1.00 and 0.95). Median MoM levels for ADAM12s were 0.90, 0.77 and 0.88 for PE, PIH and IUGR respectively; MoM levels for PP13 were 0.77, 0.95 and 0.89 respectively. ROC analysis yielded areas under the curve (AUC) for ADAM12s and PP13 of 0.63 and 0.59 for PE, 0.68 and 0.57 for PIH and 0.59 and 0.62 for IUGR, respectively. Combined ADAM12 and PP13 did not improve AUC. If specificity was set at 0.80, the corresponding sensitivity of ADAM12s was 52% for PIH.

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

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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

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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

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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