HYPERTENSION

Abstracts 71 – 78

Moderators: Donna Johnson, MD; George Saade, MD

71 Significant differences in dynamic platelet behavior in gestational hypertension and preeclampsia compared with intrauterine growth restriction suggesting alternate pathways in utero-placental disease

Sieglinde Müllers[1], Jonathan Cowman[3], Naomi Burke[1], Aoife Murray[1], Karen Flood[1], Elizabeth Tully[1], Hugh O'Connor[1], Mark Dempsey[1], Patrick Dicker[4], Michael Geary[2], Dermot Kenny[3], Fergal Malone[1]

[1]Royal College of Surgeons in Ireland/Rotunda Hospital, Obstetrics and Gynecology, Dublin, Ireland, [2]Rotunda Hospital, Obstetrics and Gynecology, Dublin, Ireland, [3]Royal College of Surgeons in Ireland, Clinical Research Centre, Dublin, Ireland, [4]Royal College of Surgeons in Ireland, Epidemiology and Public Health, Dublin, Ireland

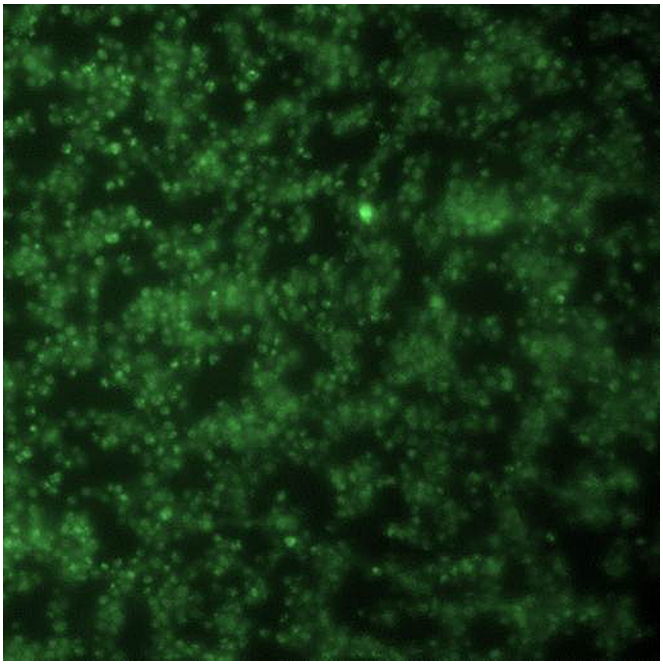
OBJECTIVE: Platelet mediated thrombosis occurs when platelets tether adhere and roll on Von Willebrand factor (vWF). We developed a novel microfluidic assay that measures these parameters thus replicating the behavior of platelets in vasculature. Using this dynamic assay of platelet function we investigated patients with preeclampsia (PET), gestational hypertension (GH) & intrauterine growth restriction (IUGR) which has never been shown to date.

STUDY DESIGN: Patients were recruited from 24wks gestation. 100ul of blood from each donor was fluorescently-labeled and perfused over a vWF coated polymer chip at arterial shear conditions. Images of platelet interactions at the surface were captured using a vacuum-cooled Andor camera. Multiple parameters of platelet behavior were assessed in each condition and all samples had a triplicate run performed.

RESULTS: 28 samples comprising of GH (n=10), PET (n=12) and IUGR (n=6) were obtained and were compared to 13 normal pregnant controls. In GH platelets demonstrated less stasis, less translocation, and less end-surface coverage compared with healthy controls ($p<0.0001$) with similar findings in PET. However, in IUGR platelets demonstrated more stasis, equal translocation and less surface coverage ($p= 0.0001$), see table.

CONCLUSION: Our novel findings show significant differences of in vivo platelet behavior in pregnancies with GH and PET in contrast to IUGR, when compared to healthy pregnant controls. In GH and PET platelets appear less reactive to the vWF surface demonstrating global hypo-reactivity. In IUGR platelets are more static suggesting a tendency to micro-thrombus formation. For the first time we have demonstrated real-time platelet activity in common pregnancy disorders. These results may challenge the theory of a homogenous pathological pathway in utero-placental disease leading to more advanced targeted platelet therapies for these conditions in the future.

Dynamic platelet assay demonstrating platelets immobilized on a surface of Von Willebrand factor



Multiple parameters of platelet function for controls, GH, PET and IUGR

	Control (n=13)	IUGR (n=6)	P value	PET (n=12)	P value	GH (n=10)	P value
Nstatic	24 +/- 12	33 +/- 11	0.016	29 +/- 23	0.33	18 +/- 11	0.02
Ntrans	211 +/- 75	216 +/- 79	0.82	185 +/- 48	0.03	164 +/- 48	0.001
%Motion	3.55 +/- 1.12	4.4 +/- 1.92	0.13	3.91 +/- 1.47	0.06	3.09 +/- 0.84	0.07
%Surface	5.97 +/- 1.5	5.17 +/- 1.83	<0.0001	5.47 +/- 1.34	0.28	4.65 +/- 0.84	0.0001

Nstatic, platelets that have not traveled more than 1.5 times their radius from the start to end of the flow run; *Ntrans*, are platelets that have traveled more than 1.5 times their radius from the start to end of the flow run; *%Motion*, the percentage of time that a platelet spends moving before stably adhering to the vWF surface; *%Surface coverage end*, the percentage of platelets (Nstatic and Ntrans) captured in the final image in comparison to the background.

72 10:12 Conjugated linoleic acid (CLA) isomer rescues HUVEC cell dysfunction in a preeclamptic in-vitro model

Nauman Khurshid[1], Derek Boeldt[2], Amanda Hankes[2], Jennifer Krupp[3], Dinesh Shah[1], Ian Bird[1]

[1]University of Wisconsin School of Medicine and Public Health, Dept. of OB/GYN, Maternal-Fetal Medicine, Madison, WI, [2]University of Wisconsin School of Medicine and Public Health, Dept of OB/GYN, Perinatal Research Branch, Madison, WI, [3]University of Iowa, Dept. of OB/GYN, Maternal Fetal Medicine, Iowa, IA

OBJECTIVE: To show 10:12 CLA isomer rescues vascular endothelial growth factor (VEGF) induced endothelial dysfunction in a human cell culture model.

STUDY DESIGN: During pregnancy greater nitric oxide release by endothelial cells is achieved via more sustained endothelial Ca2+ bursting which in turn is due to increased gap junction complexes (Cx43) between cells. In preeclampsia, such enhanced Ca2+ bursting is missing (In press) and in both ovine and HUVEC cells, factors such as VEGF can inhibit sustained Ca2+ bursts by activating intracellular kinases that phosphorylation and close/disassemble junctional Cx43 complexes. 10:12 CLA can inhibit VEGF activated kinases, and we have recently shown that 10:12 CLA is able to rescue endothelial Ca2+ bursts in an ovine model subjected to VEGF. In this study we evaluate the effect of VEGF on human umbilical vein endothelial cells (HUVEC) Ca2+ bursts and evaluated if 10:12 CLA treatment rescues Ca2+ bursts. Human umbilical vein endothelial cells (HUVEC) were grown to >90% confluence, treated with Fura-2 and imaged for Ca2+ burst first with 100uM ATP alone, followed by a wash and adding 10 ng/ml VEGF before subsequent ATP stimulation. For endothelial rescue 50uM 10:12 CLA is added to the HUVEC during the wash step before VEGF treatment. Ca2+ bursts are analyzed after second ATP stimulation and compared to internal control of first ATP stimulation.

RESULTS: 10ng/ml VEGF pretreatment inhibited periodic Ca2+ bursts in response to 100uM ATP by 45% in HUVEC ($p<0.001$). 10:12 CLA recovered Ca+2 bursts in VEGF pretreated HUVEC from 45% back to 82% of control ($p<0.001$)(Fig. 1).

CONCLUSION: CLA 10:12 isomer is able to rescue Ca2+ bursts in VEGF treated HUVEC. We report for the first time that VEGF mediated human endothelial dysfunction can be reversed by CLA. These data suggest that 10:12 CLA could potentially be the first effective agent to treat Preeclampsia related endothelial dysfunction.

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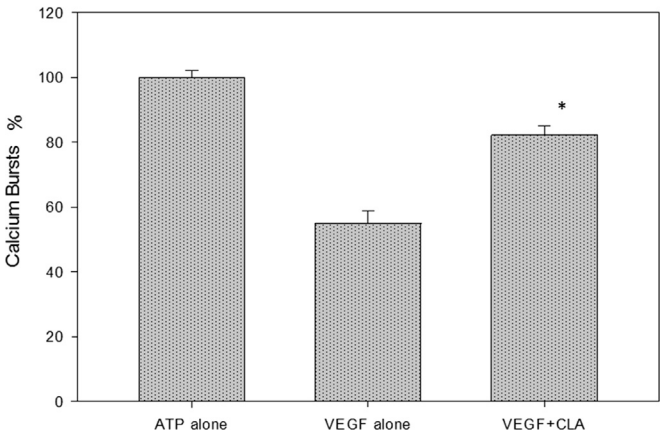
Figure 1. Calcium Burst analysis



73 Prepregnancy obesity and the risk of cause-specific stillbirth

Lisa Bodnar[1], W. Tony Parks[1], Kiran Perkins[1], Barbara Abrams[2], Maisa Feghali[1], Sarah Pugh[1], Karen Florio[1], Omar Young[1], Sarah Bernstein[1], Robert Platt[3], Hyagriv Simhan[1]

[1]University of Pittsburgh, Pittsburgh, PA, [2]University of California-Berkeley, Berkeley, CA, [3]McGill University, Montreal, QC, Canada

OBJECTIVE: Major gaps remain in our understanding of the pathophysiologic links between maternal obesity and stillbirth. Our objective was to estimate the association between prepregnancy BMI and the risk of cause-specific stillbirth.

STUDY DESIGN: In a case-cohort study, we selected all stillbirths at ≥16 weeks gestation (n=563) and a random sample of 1698 births occurring at Magee-Womens Hospital in Pittsburgh, PA from 2003 to 2010. For all cases, placental histology was examined by a perinatal pathologist and medical records were reviewed and systematically discussed by a panel of maternal-fetal medicine experts. Probable cause(s) of fetal death were assigned using the NICHD Stillbirth Collaborative Research Network Initial Causes of Fetal Death protocol. Cox proportional hazards models were used to estimate the BMI-stillbirth association after adjustment for race, maternal age, marital status, and smoking. All subjects were weighted using the inverse of the sampling fraction.

RESULTS: In the cohort, 24%, 10%, and 7.5% of mothers were overweight (25-<30), obese (30-<35) and severely obese (≥35). The unadjusted incidence of stillbirth in underweight, normal weight, overweight, obese, severely obese mothers, respectively, was 5.4, 5.7, 8.2, 10.5, 11.8 fetal deaths per 1,000 livebirths and stillbirths. After adjustment for confounders, maternal obesity was associated with all-cause stillbirth, antepartum stillbirth, and stillbirths related to hypertension; fetal genetic, structural and karyotypic abnormalities; and cord accidents (Table). Pregravid BMI was not associated with preterm labor/infection-related stillbirth. Results were not meaningfully different when hypertension- and infection-related stillbirths were limited to those with placental abruption, or when stillbirth cases were classified based on probable or possible cause.

CONCLUSION: The dramatic rise in the prevalence of obesity and severe obesity in the U.S. may increase rates antepartum stillbirths and stillbirths due to hypertension, fetal abnormalities, and cord accidents.

Association between prepregnancy body mass index category and stillbirth

	All-cause stillbirth Adj HR (95 % CI)	Antepartum stillbirth Adj HR (95% CI)	HTN-related stillbirth Adj HR (95% CI)	Preterm labor/ Infection-related stillbirth Adj HR (95% CI)	Fetal abnormality-related stillbirth Adj HR (95% CI)	Cord accident-related stillbirth Adj HR (95% CI)
Underweight	0.9 (0.5, 1.6)	0.7 (0.3, 1.5)	1.4 (0.3, 6.8)	0.9 (0.3, 2.5)	1.5 (0.5, 5.1)	0.8 (0.2, 3.6)
Normal weight	ref	ref	ref	ref	ref	ref
Overweight	1.4 (1.1, 1.8)	1.4 (1.1, 1.9)	2.4 (1.1, 4.9)	1.3 (0.8, 2.1)	1.1 (0.6, 2.3)	1.2 (0.7, 2.3)
Obese	1.7 (1.2, 2.4)	2.0 (1.4, 2.9)	3.3 (1.5, 7.8)	0.9 (0.4, 1.9)	3.0 (1.4, 6.1)	3.0 (1.6, 5.8)
Severely obese	1.8 (1.2, 2.6)	2.0 (1.1, 3.6)	3.0 (1.2, 7.7)	1.0 (0.5, 2.1)	1.5 (0.5, 4.1)	2.1 (1.0, 4.5)

74 First trimester placental and myometrial blood perfusion measured by 3D power Doppler in term and preterm preeclampsia

Suzanne Demers[1], Mario Girard[2], Amelie Tetu[2], Stéphanie Roberge[3], Emmanuel Bujold[1]

[1]Université Laval, Obstetrics & Gynecology, Quebec, QC, Canada, [2]Centre de recherche du CHU de Québec, Québec, QC, Canada, [3]Université Laval, Social and preventive medicine, Quebec, QC, Canada

OBJECTIVE: To evaluate the vascularization of the placenta and the sub-placental myometrium at 11-13 weeks in women who will develop term or preterm preeclampsia.

STUDY DESIGN: A case-control study nested in a prospective cohort study was conducted in women with singleton pregnancy undergoing an 11-13 weeks ultrasound. A three-dimensional (3D) standardized acquisition of the placenta and the subplacental