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First Trimester Prediction of Uteroplacental Disease- Results of the Prospective Handle Study

Kathy Monteith
RCSI Dublin, Ireland

Lisa McSweeney
RCSI Dublin, Ireland

Colm R. Breathnach
RCSI Dublin, Ireland

Lucy Sherrin
RCSI Dublin, Ireland

Patrick Dicker
RCSI Dublin, Ireland

See next page for additional authors

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Authors
Kathy Monteith, Lisa McSweeney, Colm R. Breathnach, Lucy Sherrin, Patrick Dicker, Elizabeth C. Tully, John O'Loughlin, Sharon Campbell, Greg Byrne, Fergal Malone, Afif EL-Khuffash, Etaoin Kent, and Ann Doherty

331 First trimester prediction of uteroplacental disease- results of the prospective handle study

Cathy Monteith[1], Lisa McSweeney[1], Colm R. Breathnach[1], Lucy Shirren[1], Patrick Dicker[1], Elizabeth C. Tully[1], John O'Loughlin[2], Sharon Campbell[2], Greg Byrne[3], Fergal D. Malone[1], Afif EL-Khuffash[2], Etaoin Kent[2], Ann Doherty[2]
[1]RCSI, Dublin, Ireland, [2]Rotunda Hospital, Dublin, Ireland, [3]Dublin Institute of Technology, Dublin, Ireland

OBJECTIVE: To assess the ability of non-invasive cardiac output monitoring (NICOM®), a novel method of non-invasive maternal hemodynamic assessment using bioreactance, in combination with first trimester biomarkers to predict the evolution of gestational hypertension (GH), pre-eclampsia (PE) and normotensive fetal growth restriction (FGR).

STUDY DESIGN: Low risk nulliparous women were enrolled in a single center prospective observational study. NICOM® assessments were performed at 14 weeks' gestation and data obtained on cardiac output (CO), indexed CO (adjusted for maternal body surface area; COI), total peripheral resistance (TPR), indexed TPR (adjusted for maternal body surface area; TPRi), stroke volume (SV), indexed SV (adjusted for maternal body surface area; SVi) and heart rate (HR). Maternal serum samples were obtained in the first trimester and the following markers were analysed: placental growth factor (PLGF; Cobas Roche); soluble fms-like tyrosine-1 (s-flt-1; Elecsys®) Apelin 13 (Nori® ELISA) and mean platelet volume (MPV). Corrleation between cardiac variables and biomarkers was assessed using Spearman coefficient. Discriminant analysis was employed to model GH, PE and FGR with NICOM® and biomarker measurements as predictors. Logistic regression was performed on variables of interest via SAS version 9.0.

RESULTS: The haemodynamic profile of pregnancies complicated by uteroplacental disease- GH (n=13), PE (n=5) and FGR (n=18) were compared to 61 healthy unaffected pregnant controls.Apelin 13 demonstrated a negative correlation with TPRi (r=-0.29, p=0.004), and a positive correlation with COi (r=0.29, p=0.005). In the prediction of PE s-flt-1 and MPV had a combined prediction model AUC 0.88 (p=0.01). Whereas in the prediction of FGR s-flt-1, SV and TPRI had a combined prediction model AUC 0.76 (p=0.007).

CONCLUSION: Apelin 13 is an inodilator produced by the normal placenta in pregnancy. This study shows the hemodynamic effects of Apelin 13 are present as early as 14 weeks' gestation. Down regulation of placental Apelin 13 has been linked with PE and lower serum Apelin with FGR, from 20 weeks' gestation onwards. However, this association was not present at 14 weeks' gestation. In addition to its known use in PE, first trimester s-flt-1 may have an role in the prediction of FGR which is strengthened by the addition of hemodynamic variables.

Table 1. Multi-logistic regression analysis in the prediction of uteroplacental disease
PET

	Individual Predictors		Combined Predictors	
	AUC	P-value	AUC	P-value
SFLT	0.69	0.155	0.88	0.011
MPV	0.76	0.103		

FGR

	Individual Predictors		Combined Predictors	
	AUC	P-value	AUC	P-value
SFLT	0.61	0.098	0.76	0.007
SV	0.59	0.148		
TPRI	0.52	0.628		

332 Can a point-of-care hemoglobin device replace complete blood count for fetal blood sampling during intrauterine transfusion?

Cathy Monteith[1], Jahan Jadauji[1], Hala Abu[1], Ann M. McHugh[1], Jennifer C. Donnelly[2], Ciaran Mooney[2], Siobhan Enright[2], Niamh Hayes[2], Fergal D. Malone[1]
[1]RCSI, Dublin, Ireland, [2]Rotunda Hospital, Dublin, Ireland

OBJECTIVE: Our objective was to prospectively validate a Point-of-Care (POC) hemoglobin device (Hemocue 201 DM system) as an alternative to a laboratory based complete blood count (CBC) in the setting of hemoglobin evaluation during cordocentesis and intrauterine fetal transfusion.

STUDY DESIGN: This prospective study was performed in a tertiary level maternity hospital. Fifteen consecutive cases of fetal anemia attending the hospital for cordocentesis and intrauterine fetal transfusion over an 18 month period were included. At the time of cordocentesis all participants had at least two episodes of dual fetal blood sampling with both a POC Test and a laboratory-based CBC. Statistical analysis was performed via Pearson's test.

RESULTS: Fifteen cordocentesis procedures were performed during the 18 month period yielding a total of 35 paired samples. There was strong correlation between the POC hemoglobin and a CBC hemoglobin with r=0.976 (95% CI 0.952-0.988) and a p value <0.0001. This study demonstrated a linear fit between both methods of hemoglobin quantification enabling the prediction of the anticipated CBC hemoglobin from CBC hemoglobin via the equation Hemocue Hemoglobin = 2.902 + 0.9617 Laboratory Hemoglobin.

CONCLUSION: Overall there is good agreement between the POC fetal hemoglobin and the CBC fetal hemoglobin. This suggests that the Hemocue 201 DM system is a viable and reproducible alternative form of measurement of fetal hemoglobin, with the important advantage of providing expedited results at the bedside. This ultimately may reduce fetal morbidity associated with cordocentesis and intrauterine transfusion, minimizing the time required to complete the procedure.

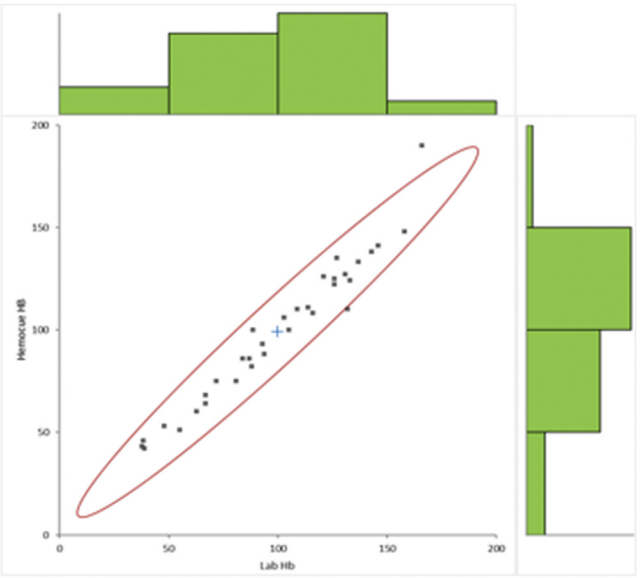

Figure 1. Correlation plot between Point-of-Care hemoglobin and a laboratory-based hemoglobin

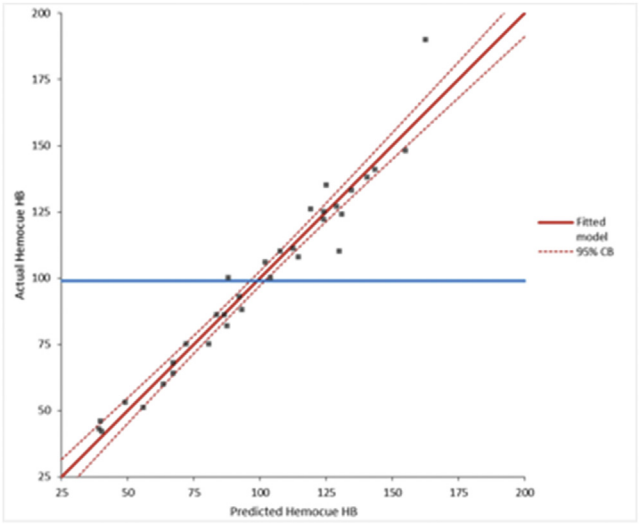

Figure 2. Hemocue prediction model based on Hemocue Hemoglobin = 2.902 + 0.9617 Laboratory Hemoglobin.

333 Potential preeclampsia therapy tested

Asif Ahmed, Keqing Wang, Shakil Ahmad, Homira Rezai
Aston Medical School of Aston University, Birmingham, United Kingdom

OBJECTIVE: Low circulating levels of placenta growth factor (PlGF) is strongly associated with the onset of preeclampsia. Although, PlGF-deficient mice are born healthy and fertile at a Mendelian ratio, the physiological importance of PlGF in the pathogenesis of preeclampsia is unclear. We hypothesised that decreased levels of PlGF in pregnancy exacerbates the fetal growth restriction associated with preeclampsia in the presence of high soluble Flt-1 (sFlt-1). Earlier studies showed that heme oxygenase-1 (HO-1) pathway inhibits sFlt-1 and as hydrogen sulfide (H_2S) stimulates HO-1, we argued H_2S donors will recuse the defects.

STUDY DESIGN: Pregnant $PlGF^{-/-}$ mice were injected with adenovirus encoding sFlt-1 (Ad-sFlt-1) at high (i) $1.5x10^9$ pfu/ml and low (ii) $0.5x10^9$ pfu/ml doses. Mean arterial blood pressure (MBP), biochemical and histological assessments of maternal kidney, placenta and embryos were performed.

RESULTS: Ad-sFlt-1 significantly increased MBP and induced severe glomerular endotheliosis in $PlGF^{-/-}$ mice at E10.5 gestation compared to wild-type animals. High sFlt-1 also significantly elevated albumin-creatinine ratio and increased levels of urinary kidney injury molecule-1, a marker for proximal tubule injury. At a high dose of sFlt-1, there was complete fetal resorption in the pregnant $PlGF^{-/-}$ mice, and even the lower dose of sFlt-1 induced severe fetal resorption and abnormal placental vascularization. H_2S-releasing agent, GYY4137, significantly reduced resorption, hypertension and proteinuria in Ad-sFlt-1 treated pregnant $PlGF^{-/-}$ mice. To determine if placental PlGF is critical for preventing fetal growth restriction associated with preeclampsia, we generated haploinsufficient $PlGF^{+/-}$ placentas and embryos were generated in wild-time dams and exposed to high sFlt-1 environment. This resulted in reduced fetal resorption, gestational hypertension and proteinuria when compared to pregnant $PlGF^{-/-}$ mice.

CONCLUSION: Placental PlGF is a critical protective factor against the damaging effects of high sFlt-1 associated with preeclampsia and activation of the H_2S pathway appears to rescue preeclampsia phenotype even under low PlGF environment possibly by upregulating other protective pathways such as the HO-1/CO system.

334 Preeclampsia with severe features: Is Ibuprofen dose associated with elevated blood pressures postpartum?

Jonathan S. Hirshberg, Shahroz Fatima, Julia D. López, Methodius G. Tuuli, George A. Macones, Alison G. Cahill
Washington University School of Medicine in St. Louis, St. Louis, MO

OBJECTIVE: The American College of Obstetricians and Gynecologists (ACOG) Task Force statement on Hypertension in Pregnancy recommends that clinicians withhold nonsteroidal anti-inflammatory medications in patients with postpartum hypertension. We sought to determine if there was a dose dependent association between Ibuprofen dose and blood pressures postpartum in those with preeclampsia with severe features.

STUDY DESIGN: This was a planned secondary analysis of a prospective cohort study of consecutive term patients meeting diagnostic criteria for preeclampsia with severe features delivered at a single academic medical center. Ibuprofen dose, frequency and time of administration were collected during the postpartum course. Noninvasive measurements of systolic and diastolic blood pressures (NIBP) were used to calculate daily mean arterial pressure (MAP). Association between Ibuprofen dose and MAPs were estimated using parametric T-tests.

RESULTS: Of the 335 patients in our analysis, 94% received Ibuprofen postpartum. For those that received Ibuprofen, there was no association between daily Ibuprofen dose and mean postpartum MAP (Figure). The median total dose of ibuprofen was 3g during the postpartum hospitalization. Patients who received more than 3g of ibuprofen had an average MAP of 100.5±9.1 mmHg, which did not differ significantly from those who received less than 3g (99.4±9.4 mmHg, p= 0.28). This relationship persisted across modes of delivery (Table).

CONCLUSION: There is no association between postpartum ibuprofen use with standard dosing and mean arterial blood pressure in patients with preeclampsia with severe features.

Table. MAPs postpartum across median ibuprofen dosage group

	Ibuprofen dose > 3g (n=132)	Ibuprofen dose ≤ 3g (n= 183)	P
Overall mean MAPs postpartum	100.5 ± 9.1	99.4 ± 9.4	0.28
Mode of delivery			
Vaginal/operative vaginal delivery	101.0 ± 9.0	99.1 ± 9.5	0.16
Cesarean	100.0 ± 9.4	101.6 ± 7.5	0.49