METABOLITE BIOMARKERS FOR EARLY PREDICTION OF PRE-ECLAMPSIA IN WOMEN WITH OBESITY

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INTRODUCTION

Pre-eclampsia (PE), a disorder specific to pregnancy, is one of the principal causes of maternal and neonatal morbidity with a prevalence of 3-5%. The cause of PE remains unclear but certain co-morbidities, such as obesity, predispose women to an increased risk[1]. Currently, all obese pregnant women are considered at equal high risk with respect to complications in pregnancy and birth, and therefore often managed through resource-intensive care pathways. More informed risk stratification of these pregnancies, would open the possibility of offering risk-appropriate integrated care.

We previously reported that early pregnancy risk factors for PE differ in obese and non-obese women[2], suggesting that several subtypes of PE may exist. Here, using a library of quantitative mass spectrometry (MS) assays for metabolites implicated in PE, we investigated predictive early pregnancy biomarkers from participants in the UPBEAT cohort of pregnant women with obesity[3]. As part of assessing the robustness of the predictors identified, secondary analyses to predict PE in various patient sub-groups and sub-outcomes was performed.

METHODS

Study samples. Prospective clinical samples (n=715) were collected from pregnant women with singleton pregnancy at first visit (16 ± 1.5 weeks gestation), who later developed PE or not (controls) (Table 1, Figure 1). PE was defined according to ISSHP 2001 criteria.

TABLE 1. Baseline characteristics of the study population

Characteristics	Controls (n=645)	PE (n=65)
Mother age	30.4 (5.49)	30.4 (4.99)
Parity		
Nulliparous	287 (45%)	38 (58%)
Multiparous	358 (56%)	27 (42%)
BMI (median, IQR)	35.1 (32.8-38.4)	37.4 (33.1-41.3)*
Morbid obesity (BMI>40)	111 (17%)	20 (31%)
Ethnicity		
Asian	32 (5%)	4 (6.2%)
Black	132 (20%)	12 (18%)
White	446 (69%)	44 (68%)
Development of GDM*	169 (26%)	18 (28%)
Preterm PE	NA	13 (20%)

*GDM: Gestational Diabetus Mellitus; *:p<0.05

FIGURE 1. Sample analysis

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Exposures. An MS assay library containing 54 metabolites (44 fulfilled quality control criteria, Figure 2), placental growth factor (PlGF), triglycerides and simple clinical risk factors (maternal age, PE in previous pregnancy, family history of PE, blood pressure and BMI) were used for predictor analysis.

Metabolites quantifications were only considered for univariable and multivariable analyses if the data missing rate across the study for a metabolite of interest ≤20% AND if %CV ≤25%. All metabolite and protein quantification data were log-transformed.

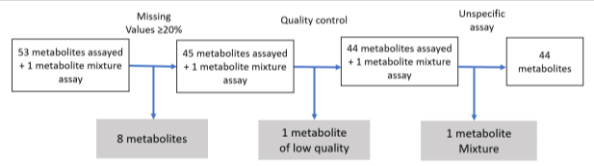

FIGURE 2. Selection of metabolites for biomarker analysis

Single marker analysis

- Univariable prognostic performance was quantified using AUROC; variables with AUROC≥0.60 and a lower limit of the 95% confidence interval of AUROC≥0.50 were deemed of interest.

Sub-group analysis

- Interaction with patients characteristics (parity, morbid obesity (bmi>40), ethnicity) and specific outcomes (GDM status, preterm PE) was explored. The significance in difference between AUROCs was tested using Delong's method.

Multivariable analysis

- The additive prognostic potential of the metabolites with univariable performance for prediction of PE in the complete cohort was compared to that of routine factors alone (clinical and PlGF). Predictors selected in the single marker analysis were used to develop multivariable predictive models (PLS-DA, selection base on Mann Whitney U test, likelyhood ratio and AUC).

RESULTS

Univariable analysis revealed 11 predictors for prediction of PE in obese with AUROC ranging from 0.60 to 0.68, with mean diastolic and systolic blood pressure (mean of 2 measurements) being the most predictive (Figure 3a).

- Sub-group analysis: Bilirubin, Biliverdin and L-arginine are highly specific to predicting PE in the morbidly obese women, as a distinct subgroup in the obese pregnant. Strikingly, NG-Monomethyl-L-arginine, is specifically not a predictor of PE in the morbidly obese; its predictive performance for PE is restricted to the non-morbidly obese pregnant women. Also, the data confirms that PlGF is more specific to predicting preterm PE in obese pregnant women compared to term PE (Figure 3b).

Multivariable analysis. Figure 3c shows exemplary combinations of 2 to 4 predictors that met the stringent performance and improvement criteria.

Although a trend of increased predictive performance with the addition of metabolites biomarkers was observed, the difference did not reach statistical significance when compared to the routine model (PlGF and blood pressure).

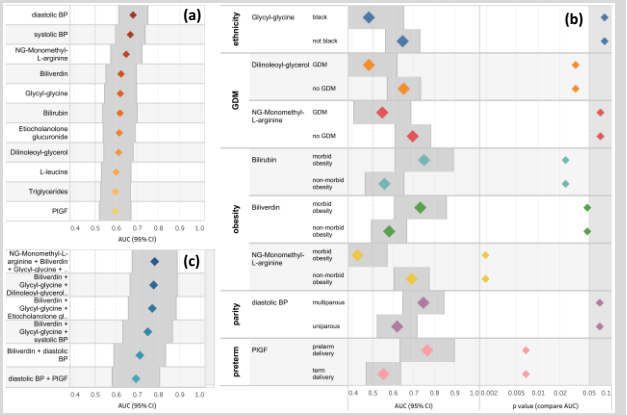

FIGURE 3.
a) A list of the 11 most predictive biomarkers by univariable analysis.
b) Predictive performance of risk factors in different subgroups by univariable analysis
c) Combinations of 1 to 4 most predictive biomarkers by multivariate analysis

GDM: Gestational Diabetes Mellitus; AUC: Area Under the Curve

CONCLUSIONS

- Here we confirm that clinical factors and biomarkers can be used to refine the assessment of PE risk in obese pregnant women.
- Our preliminary data also suggest that PE within the obese may be heterogeneous and that different sub-types of PE can develop.
- Further studies are needed to verify these initial observations, and whether a different set of predictors in conjunction with patient phenotypic characteristics, can be used to deliver more accurate PE predictions for obese pregnant women.

[1]Poston et al, Lancet Diabetes Endocrinol 2016, 4(12):1025. [2]Vieira et al, Obesity 2017,25:460. [3]Poston et al, Lancet Diabetes Endocrinol 2015, 3(10):767.