Objective
Term PE (tPE) is the most common, poorly understood and the most difficult group to predict form of PE. Our objective was to elucidate the mechanisms of and predict term preeclampsia (tPE) (≥37weeks) using serial integrated (combined first and third trimester) metabolomic and proteomic approaches.

Methods
First (11-14 weeks) and third (30-34 weeks) trimester serum samples obtained prior to development of tPE, were analyzed using targeted metabolomic (1H NMR and DI-LC-MS/MS) and proteomic (MALDI-TOF/TOF-MS) platforms. In total, 35 tPE cases and 63 controls were analyzed. Stepwise logistic regression analysis was used to generate predictive models for each and combined trimesters. Integrated pathway over-representation analyses were performed and latent relationships between metabolites and peptides were further mapped by constructing a network analysis. Area under the ROC curve (AUC) (95% CI) was calculated.

Results
Serial first (sphingomyelin C18:1 and urea) and third trimester (hexose and citrate) metabolites predicted tPE with an area under the ROC curve (AUC) (95% CI) = 0.817 (0.732-0.902) and a sensitivity of 81.6% and specificity of 71.0%. Serial first [TATA box binding protein-associated factor (TBP)] and third trimester [Testis-expressed sequence 15 protein (TEX15)] protein biomarkers highly accurately predicted tPE with an AUC (95%CI) of 0.987 (0.961-1.000), sensitivity 100% and specificity 98.4%. Commonly utilized demographic, history and clinical markers did not improve prediction over omics markers alone. Integrated pathway overrepresentation analysis using metabolomic and proteomic data revealed significant alterations in signal transduction, G protein coupled receptors, serotonin and glycosaminoglycan metabolisms which were further mapped to perturbed lipid, energy and N-glycan metabolisms using the network analysis. Literature review confirmed a known, suspected or plausible role of these biological pathways with PE development.

Conclusion
This is the first report integrating metabolomic and proteomic analysis of PE. Novel insights into disease pathogenesis and high predictive accuracy for tPE were achieved.