First-trimester Metabolomic Prediction of Subsequent Stillbirth
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Objective
To develop and evaluate new metabolomic biomarkers first-trimester maternal serum biomarkers for predicting stillbirth (SB).

Methods
Targeted i. e. Nuclear Magnetic Resonance (NMR) and Mass Spectrometry (MS), and untargeted metabolomic analyses were performed in an average risk group. Case-control analysis was done in 60 cases that subsequently had a subsequent SB and 120 controls. Metabolite markers by themselves or in combination with β-hCG, PAPP-A, demographic characteristics, history and other clinical risk factors such as uterine artery Doppler, were used to develop algorithms for stillbirth prediction using logistic regression. Sensitivity, specificity, areas under the curve (AUC) and 95% confidence intervals (CI) were calculated. Prediction of overall SB, those occurring at < 32 weeks (early), those related to growth restriction/placental disorder and unexplained stillbirths were evaluated.

Results
Fully identified metabolite based markers predicted overall stillbirth with good accuracy: AUC (95% CI): 0.707 (0.628-0.785). When combined with clinical predictors this increased to 0.740 (0.667-0.812) with a sensitivity 90.0%. For early stillbirth using a combination of serum metabolites with other markers, the sensitivity was 90.9%. First-trimester metabolites also predicted unexplained (81.8% sensitivity) and placental-related stillbirths (86.7% sensitivity). Untargeted analysis yielded additional biomarkers, including a household toxin, that predicted SB with an AUC (95% CI)= 0.860 (0.793-0.927) and 95.5% sensitivity.

Conclusion
We have identified some completely novel serum biomarkers for stillbirth and demonstrated the feasibility of first-trimester prediction.