Preterm Preeclampsia Screening: Combining Phenotypic Biomarker Models into Robust Prediction Models

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OBJECTIVES

To investigate if preterm preeclampsia prediction can be improved with metabolite biomarkers in three screening resource scenarios:

1. availability of Placental Growth Factor (PIGF),
2. availability of PIGF + Mean Arterial Pressure (MAP)
3. availability of PIGF, MAP + Uterine Artery Pulsatility index (UTA-PI),

using a patient classification in combination with a purpose-developed machine learning predictor modelling methodology.

BACKGROUND

- Preeclampsia (PE) screening is a key component of antenatal care.
- Current benchmark for PE screening[(1)] (Figure 1)
  - is performed at 11^{+0} -13^{+6} weeks' gestation
  - detects 75% of women developing PE with a delivery <37 weeks (preterm PE)
  - allows for timely initiation of aspirin prophylaxis, i.e., ≤16 weeks[(1)].
  - Universal implementation is hampered by insufficient availability of and access to prenatal care experts.
- To improve PE screening further additional biomarkers are required.

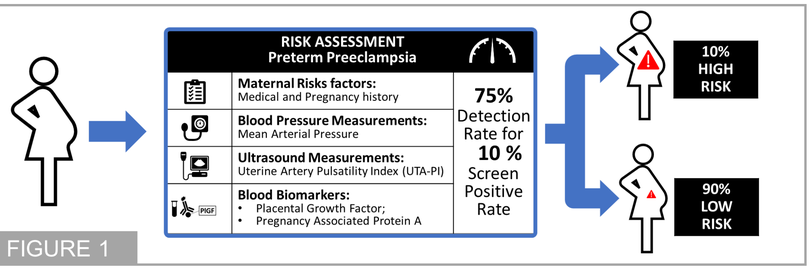

FIGURE 1

- **Recent findings:**
  - early pregnancy metabolite levels associate with preterm PE;
  - metabolite associations with preterm PE prediction can vary according to maternal body mass index (BMI)[(2)].
- **Hypothesis:** Use of patient classification enables a more effective combination of biomarkers and thus improved preterm PE risk prediction (Figure 2).

- Recent research suggests the existence of distinct maternal risk profiles associated with different maternal phenotypes[(3)].
- Biomarker application should therefore account for the possibility that biomarkers only predict PE in a specific maternal phenotype.

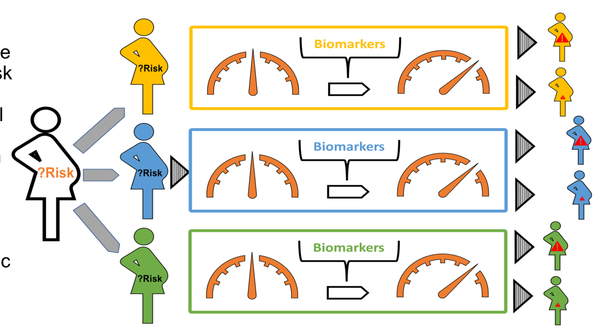

FIGURE 2

Rolnik DL et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. N Engl J Med. 2017;377(7):613–22. (2) Tuytten R et al. First Trimester Preterm Preeclampsia Prediction with Metabolite Biomarkers: Differential Prediction According to Maternal Body Mass Index. Am J Obstet Gynecol. https://doi.org/10.1016/j.ajog.2022.12.012. (3) Than NG et al. Integrated Systems Biology Approach Identifies Novel Maternal and Placental Pathways of Preeclampsia. Front Immunol. 2018;9

STUDY POPULATION

Characteristic	preterm PE (n= 106)	Controls (n= 1635)
Gestational age at sampling (wk)	12.6 (12.22, 12.98)	12.7 (12.3, 13.0)
Maternal age (y)	30.5 (27.5, 35.4)	32.1 (28.4, 35.5)
Ethnicity [a]		
White	48 (45.3)	1025 (62.7)
Black	51 (48.1)	433 (26.5)
South Asian	4 (3.8)	66 (4.0)
East Asian	1 (0.9)	52 (3.2)
Mixed	2 (1.9)	59 (3.6)
Height (cm)	164 (160, 167)	165 (160, 169)
Weight (kg)[a]	75.2 (65.8, 87.0)	65.4 (59.0, 75.7)
Body mass index class (kg/m^2)[a]		
<18.5	1 (0.9)	33 (2.0)
18.5 to <25	32 (30.2)	911 (55.7)
25 to <30	33 (31.1)	419 (25.6)
³30	40 (37.7)	272 (16.6)
Gestational age at delivery (wk)[a]	34.2 (31.6, 35.7)	39.2 (38.7, 39.5)
Birth weight (g)[a]	1771 (1354, 2093)	3295 (3100, 3515)
Birth weight percentile (%)[a]	0.48 (0.03, 10.14)	47.13 (29.19, 66.87)

Data are represented as median (interquartile range) or number (percentage).
[a]: Chi-square or Mann Whitney U test as appropriate (p <.01).

STUDY DESIGN

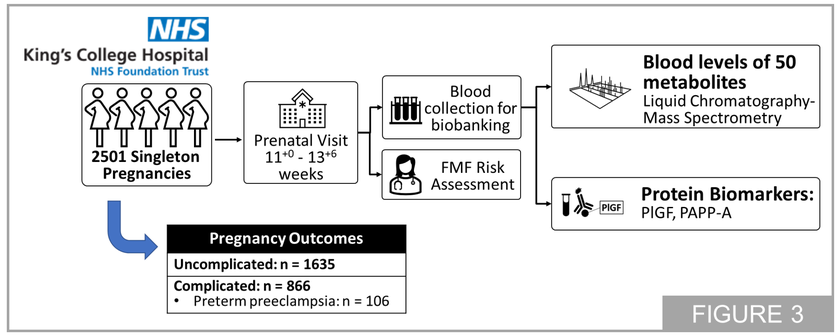

FIGURE 3

METHODS

- Biomarker data were normalized using multiples of medians
- Model development: (1) in all patients, (2) BMI and/or race patient strata Modelling methodology to generate prediction model:
  1. z-score conversion of predictors,
  2. combinatorial modelling of single predictive models
  3. selection of single sparse models, and
  4. aggregation of the selected models into final prediction model.
- Model Prediction performance evaluation: detection rate at 10% FPR

RESULTS

- Modelling methodology validation: Splitting the patient set into a training (2/3) and a test (1/3) set showed developed models were not overfitted.
- 3 Prediction models were developed using the complete data set in accordance with the three resource scenarios investigated.
- 26 Metabolites were used across the 3 prediction models; 21 contributed to at least 2 out of 3 prediction models developed.
- Detection rates were markedly higher with the prediction models than with the respective reference models (Figure 4), whereby
  - The largest improvements were observed in scenario 2, with a 15% increase over the detection rate estimated for the reference PIGF + MAP.
  - Prediction was improved in Black (14%) and White (19%),
  - Prediction was improved in the normal weight (18.5≤ BMI <25) and the obese groups (BMI ≥30), but not in In the overweight group (25≤ BMI < 30),

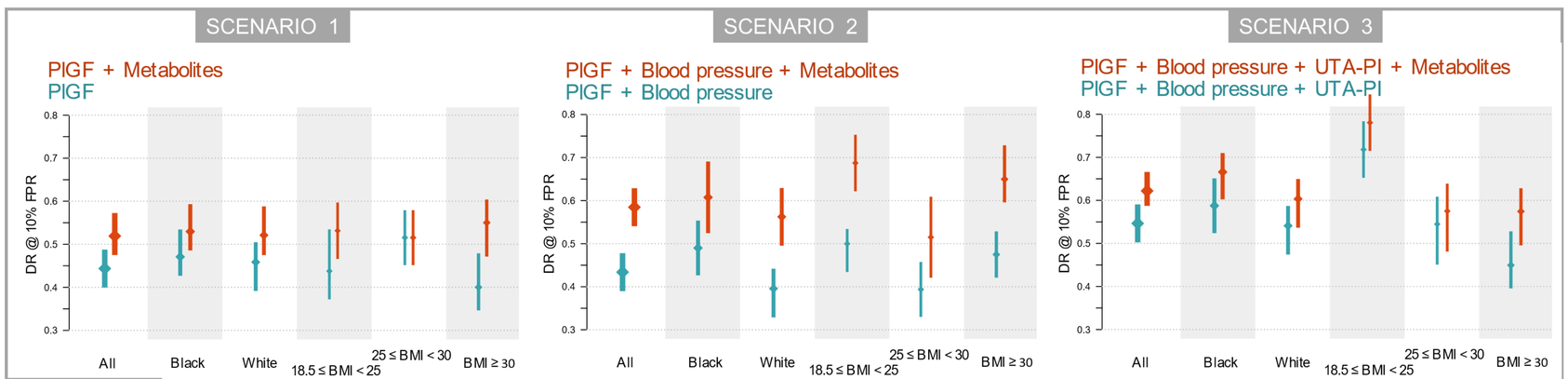

FIGURE 4

CONCLUSIONS

Metabolite biomarkers can be combined with the established biomarkers PIGF, MAP and UTA-PI to improve the detection of preterm PE risk in a clinically useful way. Pivotal to achieving improved prediction was the classification of pregnant women according to the maternal characteristics of BMI and/or race. This suggests that maternal phenotyping can have a role in improving the prediction of obstetric syndromes like PE.