LIQUID BIOPSY THROUGH MATERNAL PLASMA CELL-FREE RNA ENABLES EARLY PREDICTION OF PREECLAMPSIA SUBTYPES

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OBJECTIVE

To evaluate the potential of maternal plasma cell-free RNA (cfRNA) as a non-invasive liquid biopsy for the early prediction of early- and late-onset preeclampsia (EOPE and LOPE), offering an alternative to combined screening strategies whose performance remains highly variable and operator-dependent.

MATERIAL AND METHODS

We conducted a multicenter, prospective case-control study across 14 Spanish hospitals (NCT04990141). A total of 9,586 pregnant women were enrolled, with cfRNA sequencing performed on 548 plasma samples collected from 216 participants: 42 EOPE, 43 LOPE, and 131 matched controls (Figure 1). cfRNA was sequenced and analyzed with differential abundance and pathway enrichment. Predictive models were developed through feature selection (LASSO regression), trained on 70% of the patients with cross-validation, validated internally using the remaining 30% subset and externally using an independent dataset (GSE192902). Model performance was assessed by sensitivity, specificity, and area under the ROC curve (AUC).

RESULTS

Distinct cfRNA signatures characterized EOPE and LOPE (Figure 2). In the first trimester, the EOPE model achieved 83% sensitivity, 90% specificity, and an AUC of 0.88, identifying at-risk women an average of 18 weeks before clinical onset. At the second trimester, EOPE prediction remained robust (AUC 0.89), while the LOPE model achieved 88% sensitivity, 92% specificity, and an AUC of 0.90, detecting cases 14.9 weeks prior to diagnosis. External validation confirmed consistent performance across cohorts (AUCs 0.87, 0.81, 0.77, respectively). Notably, 47.2% of EOPE predictive transcripts overlapped with decidualization resistance (DR)-related genes in the first trimester, directly linking impaired endometrial remodeling to EOPE pathogenesis. In the second trimester, the proportion of DR-related predictors accounted for approximately one-third of EOPE transcripts, supporting a persistent maternal contribution. Pathway analysis revealed subtype-specific biology, with EOPE enriched in immune and widespread tissue injury pathways and LOPE in hepatic and cardiovascular processes.

CONCLUSION

cfRNA enables accurate, non-invasive prediction of EOPE in both the first and second trimesters and LOPE in the second trimester, with validated performance across independent datasets. Although our case-control design may limit generalizability, a large-scale external validation is ongoing (NCT06716242) to assess real-world applicability.

IMPACT STATEMENT

This study demonstrates the translational potential of cfRNA as a scalable and robust tool for pregnancy complication screening, enabling earlier prevention and personalized monitoring.

CONTACT

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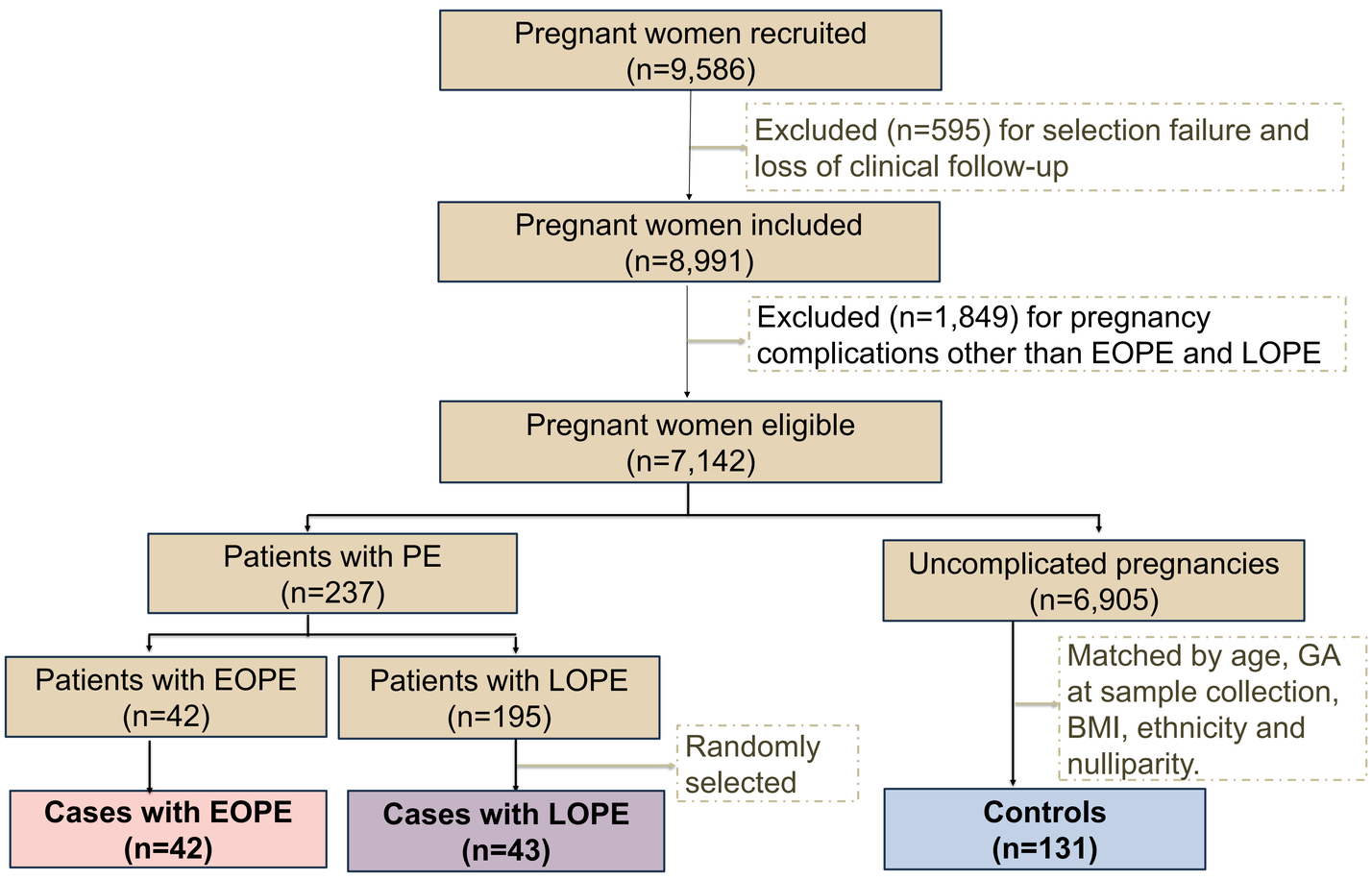

Figure 1. Flowchart of the study. A total of 9586 pregnant participants were recruited. For cfRNA analysis, we included all 42 EOPE cases, a subset of 43 LOPE cases and 131 normotensive controls, randomly selected from the matched cohort based on gestational age at sample collection, maternal age, parity, ethnicity, and BMI.

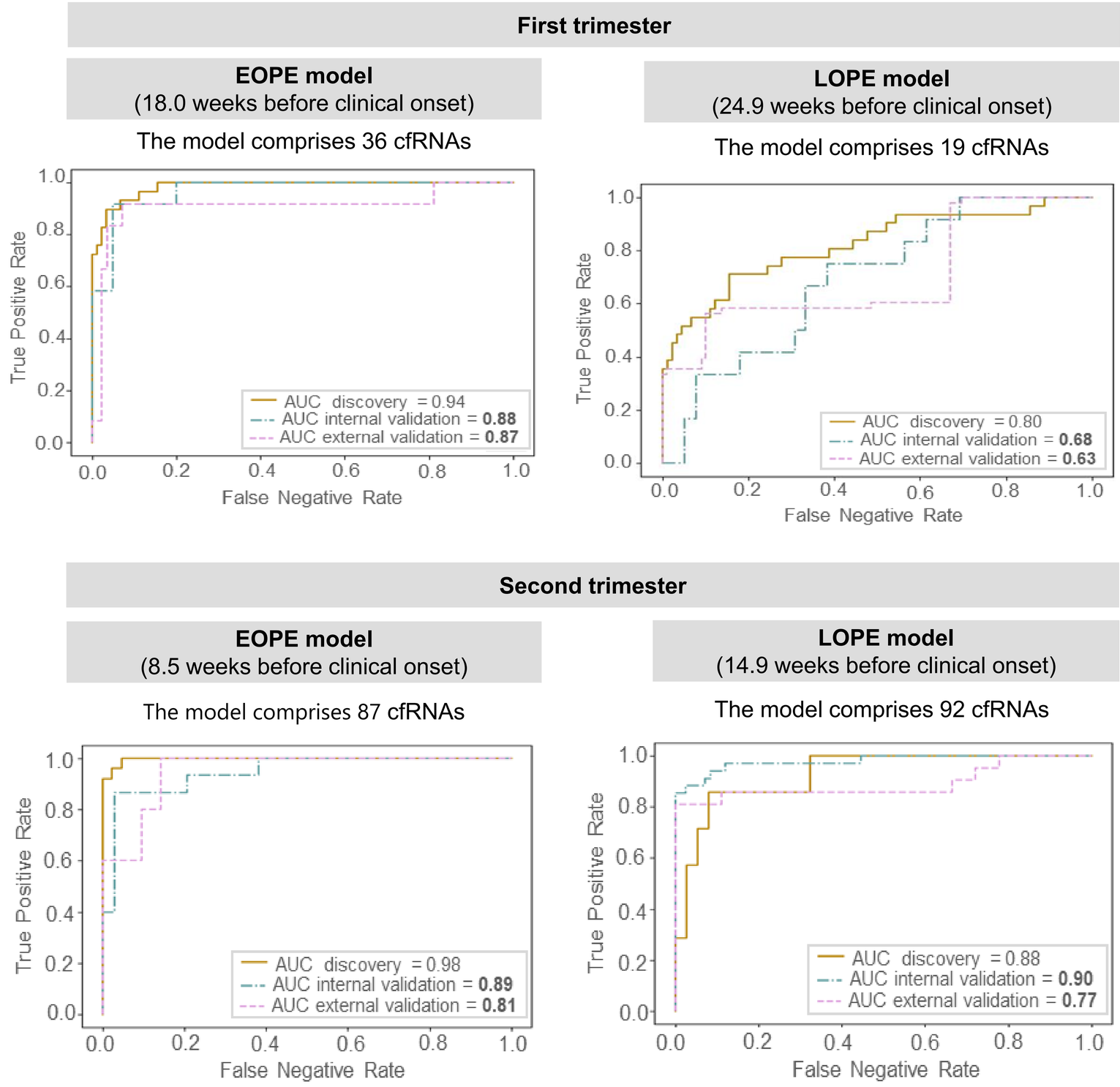

Figure 2. Performance of predictive models for EOPE and LOPE. Receiver operating characteristic (ROC) curves showing model performance for EOPE and LOPE in the first and second trimesters across discovery, internal (Validation 1) and external (Validation 2) datasets.

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