OBSTETRICS

Predictive RNA profiles for early and very early spontaneous preterm birth

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Background

Spontaneous preterm birth remains the main driver of childhood morbidity and mortality. Because of an incomplete understanding of the molecular pathways that result in spontaneous preterm birth, accurate predictive markers and target therapeutics remain elusive.

Objective

This study sought to determine if a cell-free RNA profile could reveal a molecular signature in maternal blood months before the onset of spontaneous preterm birth.

Study Design

Maternal samples (n=242) were obtained from a prospective cohort of individuals with a singleton pregnancy across 4 clinical sites at 12−24 weeks (nested case-control; n=46 spontaneous preterm birth <35 weeks and n=194 term controls). Plasma was processed via a next-generation sequencing pipeline for cell-free RNA using the Mirvie RNA platform. Transcripts that were differentially expressed in next-generation sequencing cases and controls were identified. Enriched pathways were identified in the Reactome database using over-representation analysis.

Results

Twenty five transcripts associated with an increased risk of spontaneous preterm birth were identified. A logistic regression model was developed using these transcripts to predict spontaneous preterm birth with an area under the curve =0.80 (95% confidence interval, 0.72−0.87) (sensitivity=0.76, specificity=0.72). The gene discovery and model were validated through leave-one-out cross-validation. A unique set of 39 genes was identified from cases of very early spontaneous preterm birth (<25 weeks, n=14 cases with time to delivery of 2.5±1.8 weeks); a logistic regression classifier on the basis of these genes yielded an area under the curve=0.76 (95% confidence interval, 0.63−0.87) in leave-one-out cross validation. Pathway analysis for the transcripts associated with spontaneous preterm birth revealed enrichment of genes related to collagen or the extracellular matrix in those who ultimately had a spontaneous preterm birth at <35 weeks. Enrichment for genes in insulin-like growth factor transport and amino acid metabolism pathways were associated with spontaneous preterm birth at <25 weeks (Figure).

Conclusion

Second trimester cell-free RNA profiles in maternal blood provide a noninvasive window to future occurrence of spontaneous preterm birth. The systemic finding of changes in collagen and extracellular matrix pathways may serve to identify individuals at risk for premature cervical remodeling, with growth factor and metabolic pathways implicated more often in very early spontaneous preterm birth. The use of cell-free RNA profiles has the potential to accurately identify those at risk for spontaneous preterm birth by revealing the underlying pathophysiology, creating an opportunity for more targeted therapeutics and effective interventions. ■

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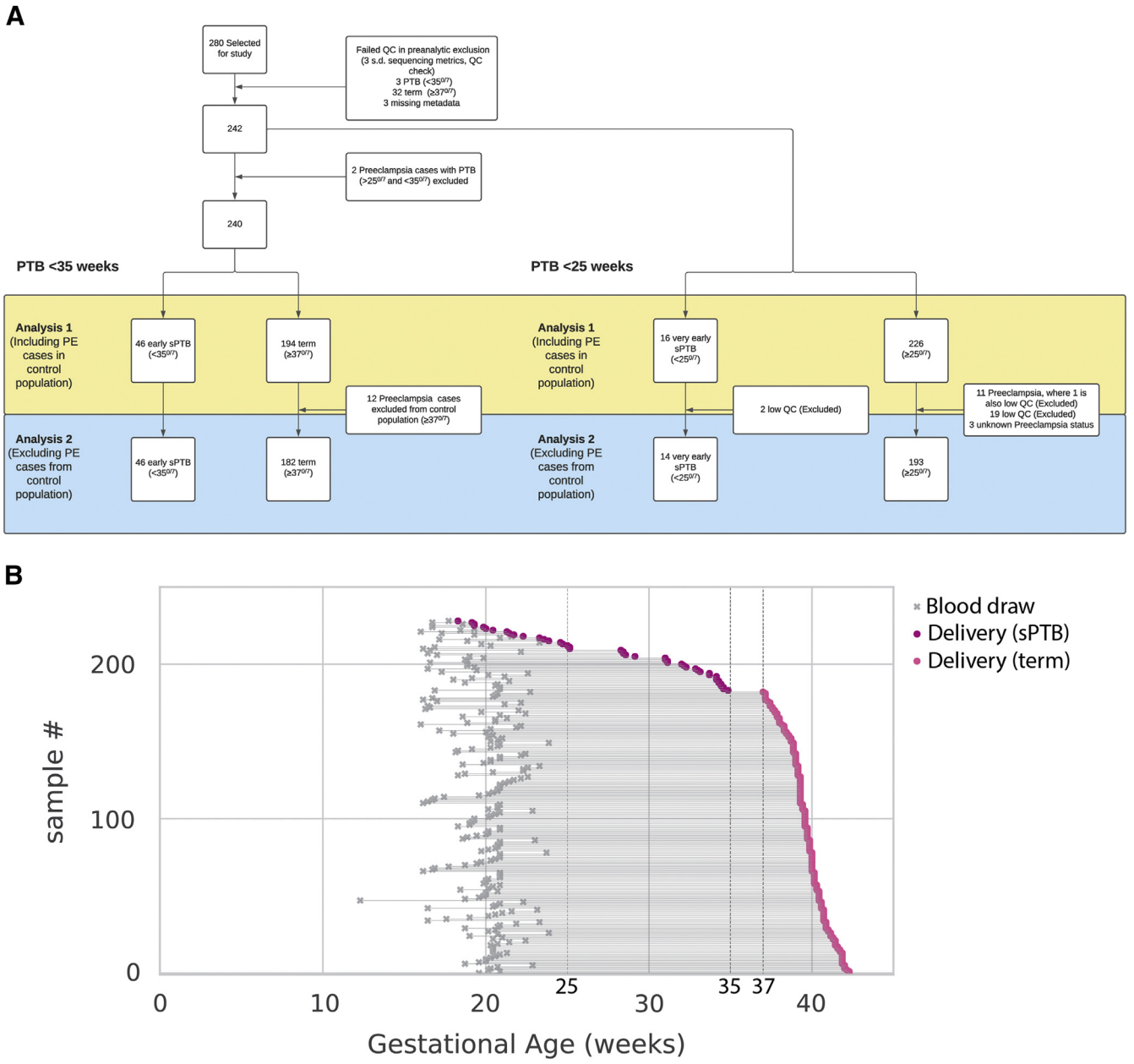
The coauthors affiliated with Mirvie are inventors of patented applications that cover the detection, diagnosis, or treatment of pregnancy complications and/or have an equity interest in Mirvie. All the cohort contributors were compensated for sample collection and/or shipping.

Samples from the "Insight: investigation into biomarkers for the prediction of spontaneous preterm birth" study were collected with support from Tommy's Charity (number

Supporting material appears on the next page

FIGURE
Study design and cohort overview



A, Diagram with study design and analysis plan; **B,** *Gray crosses* indicate GA at sample collection (blood draw), and circles indicate GA at delivery (*dark purple* for sPTB and *light purple* for at-term controls).

GA, gestational age; *sPTB*, spontaneous preterm birth.

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To protect the identity of the study participants, the data will be made available with a signed data use agreement (contact research@mirvie.com). All code is available online: https://doi.org/10.5281/zenodo.6395172.

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