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512 Discovery and verification of maternal serum miRNA biomarkers predictive of preeclampsia



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OBJECTIVE: Placental dysfunction, including preeclampsia and fetal growth restriction, is a leading contributor to maternal and fetal morbidity and mortality. Development of effective prevention and treatment strategies has been limited by lack of identification of at-risk pregnancies. We performed small RNA sequencing of maternal serum microRNAs (miRNAs) to discover and independently verify biomarkers differentially expressed in patients who later developed preeclampsia.

STUDY DESIGN: Maternal serum was collected between 17-28 weeks gestation in two cohorts: The high-risk UCSD Placenta Study (19 cases, 29 controls); and the Sera Prognostics PAPR Study (54 cases, 110 controls). Samples were divided into Discovery (2/3) and Verification sets (1/3). Cases and controls were matched for gestational age (GA) at blood draw (Table 1). miRNAs were isolated and sequenced to yield miRNA counts. Individual miRNAs and pairwise ratios (reversals) were tested in blinded verification.

RESULTS: Biomarker discovery and verification were performed on the entire GA range and for 3 GA windows: 17^{0/7} - 21^{5/7} (Early); 19^{5/7} - 24^{4/7} (Middle); and 22^{2/7} - 28^{0/7} (Late) weeks.

In Discovery, best performing miRNAs and reversals were selected for each GA window. Performance was then confirmed in blinded Verification (Table 2). 7/50 Early GA reversals had significant AUCs (mean Discovery AUC 0.78, mean Verification AUC 0.79). 21/50 Late GA reversals had significant AUCs (mean Discovery AUC 0.71, mean Verification AUC 0.68). Of biological importance, verified reversals contained a high proportion of miRNAs that were strongly expressed in placenta and/or encoded in the chr14q32 and chr19q13 miRNA clusters. miR-155-5p, present in 21 verified reversals, has been reported to mediate repression of eNOS by TNF α , which is a regulatory interaction associated with preeclampsia.

CONCLUSION: We identified and verified differentially abundant miRNAs in maternal serum at 17-28 weeks GA in pregnancies that later developed signs and symptoms of preeclampsia compared to pregnancies with uncomplicated outcomes. Our findings suggest that maternal serum miRNAs may be useful as biomarkers for prediction of placental dysfunction and warrant validation in large independent cohorts.

Table 1. Study Subject Demographics

	Training (N=141)			Verification (N=71)			p-value
	Case N=49	Control N=92	p-value	Case N=24	Control N=47	p-value	
Mean Maternal Age (years)	30.1±6.4	29.0±6.1	0.29	26.8±6.7	27.7±6.1	0.59	0.88
Mean BMI	30.7±10.1	26.1±7.8	0.02	33.7±9.6	27.6±7.5	0.01	0.95
Patients with diabetes	10 (20.4%)	9 (9.8%)	0.12	5 (20.8%)	5 (10.6%)	0.29	1.0
Race/Ethnicity							
White: Non-Hispanic	24 (49.0%)	50 (54.3%)	0.40	7 (29.2%)	20 (42.6%)	0.57	0.11
Hispanic	12 (24.5%)	25 (27.2%)		13 (54.2%)	17 (36.2%)		
African-American	7 (14.3%)	9 (9.8%)		3 (12.5%)	8 (17.0%)		
Asian	4 (8.2%)	3 (3.3%)		0 (0.0%)	1 (2.1%)		
Pacific Islander	1 (2.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)		
Other	1 (2.0%)	5 (5.4%)		1 (4.2%)	1 (2.1%)		
Median gestational at sample collection (weeks)	24.3±3.0	24.0 ±3.1	0.31	24.1±2.9	23.5±3.3	0.39	0.71
Median gestational age at delivery (weeks)	36.3±6.4	39.2±1.2	<0.01	36.2±3.2	39.3±2.5	<0.01	0.67
Birthweight (grams)	2589.5±922.7	3464.8±465.4	<0.01	2733.6±893.5	3213.0±675.9	0.03	0.87
IUGR	11 (7.9%)			5 (7.0%)			1.0

Table 2. Top ranked verified miRNA reversals per GA window.

GA Window	Numerator	Denominator	Direction (case - ctrl)	Discovery AUC	Discovery 95%CI	Verification AUC	Verification 95% CI
Full	hsa-miR-127-3p	hsa-miR-485-5p	Down / Down	0.67	0.57 - 0.76	0.67	0.55 - 0.79
Early	hsa-miR-4732-3p	hsa-miR-381-3p	Up / Down	0.82	0.69 - 0.95	0.80	0.62 - 0.98
Middle	hsa-miR-150-3p	hsa-miR-193b-5p	Up / Up	0.72	0.59 - 0.863	0.70	0.52 - 0.87
Late	hsa-miR-26b-5p	hsa-miR-155-5p	Up / Down	0.68	0.56 - 0.80	0.72	0.57 - 0.86

The top reversal is shown for each GA window. Annotations are as follows:

- Numerator: miRNA in the numerator of reversal ratio calculation.
- Denominator: miRNA in the denominator of reversal ratio calculation.
- Direction: expression is up or down in preeclampsia cases as compared to controls.

513 Obstetric outcomes for women receiving newer generation antiepileptic drugs: retrospective cohort study using claims database



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OBJECTIVE: Women with epilepsy are at increased risk for adverse pregnancy outcomes. Since the 1990s, over 11 new antiepileptic drugs (AEDs) have been introduced. We aimed to describe the use of newer AEDs in pregnancy and differences in rates of obstetric outcomes.

STUDY DESIGN: From the Truven Health MarketScan® Commercial Claims and Encounters Database (years 2011-14), we identified women who had a delivery admission, outpatient pharmacy dispenses for newer generation AEDs (Table) and an indication of epilepsy based on diagnosis codes during the 12 months prior to delivery. Obstetric outcomes included preterm birth, cesarean delivery, postpartum hemorrhage, placental abruption, hypertensive disorders of pregnancy, preterm labor, and severe maternal morbidity (SMM). We described the prevalence of the use of newer AEDs and rates of obstetric outcomes and absolute risk difference compared to women without a diagnosis of epilepsy (Table).