A Novel Panel of Midtrimester Biomarkers to Predict Preterm Labour

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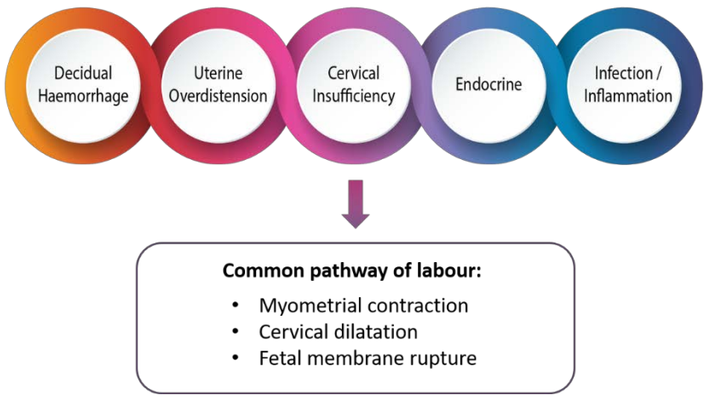
Mercy Health
Care first

INTRODUCTION

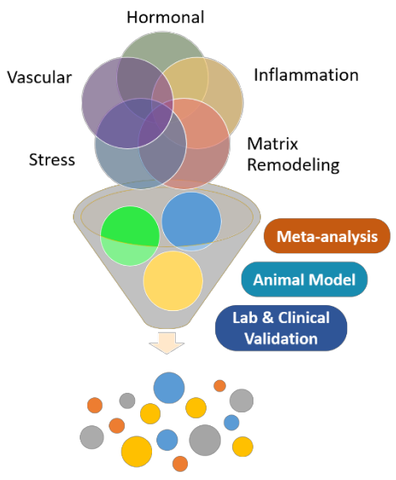
PRETERM BIRTH

Preterm birth (PTB) is defined as the birth of an infant before 37 weeks of gestation. In 2010, fifteen million infants were born preterm worldwide and over 1 million of those did not survive their first month of life. In the U.S. alone, over 450,000 babies were born preterm (1 in 9) leading to a huge economic burden of over USD 26 billion to the healthcare system. PTB is the cause for 75% of all neonatal mortality. PTB babies suffer from a wide range of systemic complications including neurological, respiratory, gastrointestinal, and infective. Long term studies have also shown autism, low educational attainment and increased burden on social welfare benefits are linked to PTB.

MULTI-FACETED ETIOLOGY

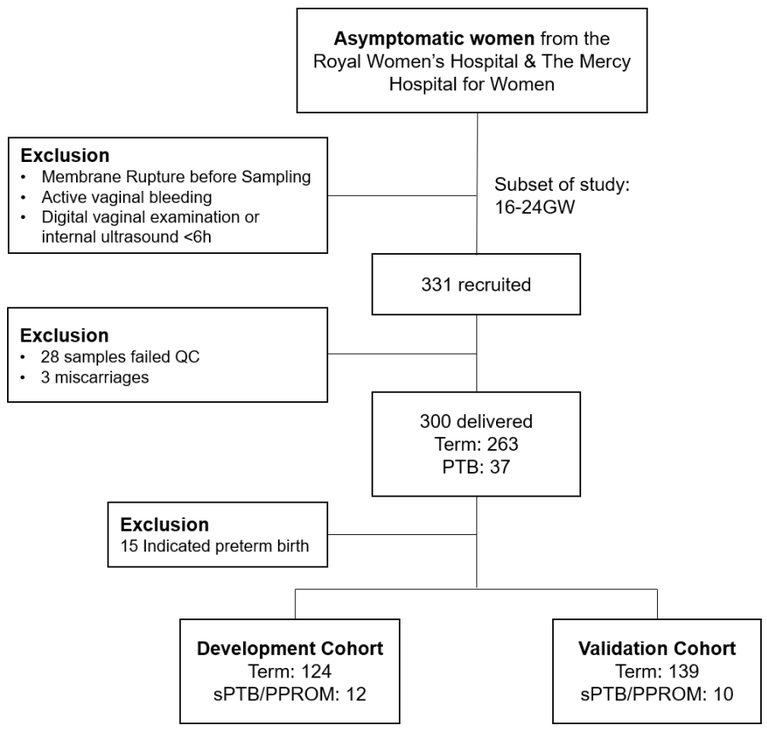


OUR TECHNOLOGY



Our panel of protein biomarkers represent the various pathways of PTB, which includes inflammation, vascularization, hormonal changes, stress, early cervical remodelling and decline in progesterone action. Through meta-analysis, bioinformatics, animal modelling and both laboratory and clinical validation, we have established proprietary biomarker combinations by incorporating a series of mini panels, each consisting of several biomarkers. To this end, we have developed an algorithm to predict women with a high risk of preterm birth with high accuracy.

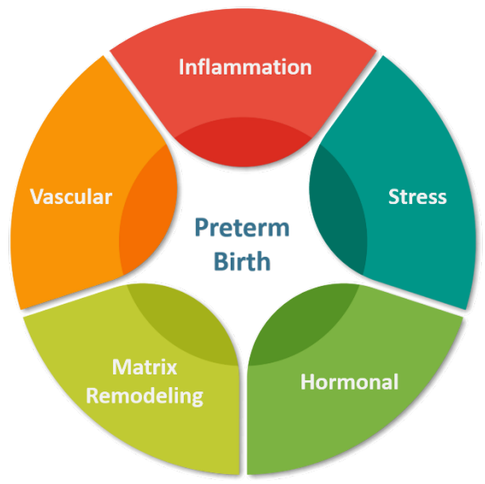
STUDY DESIGN



Participants were recruited from Royal Women's Hospital and the Mercy Hospital for Women with exclusion criteria of 1) membrane rupture before sampling, 2) active vaginal bleeding, and 3) digital vaginal examination or internal ultrasound 6h before sampling. Out of 300 participants, 15 were excluded as they had indicated preterm birth. The participants were further divided into training cohort and validation cohort based on their delivery dates.

RESULTS

BIOMARKER DISCOVERY



Inflammation
VDBP | IL-1ra

Stress
TIMP-1 | VDBP | IL-1ra

Hormonal
GGH | TIMP-1

Matrix Remodeling
PEDF | ECM1 | TIMP-1 | LAMC2

Vascular
PEDF | LAMC2

7 Novel Biomarkers to predict preterm birth in asymptomatic women

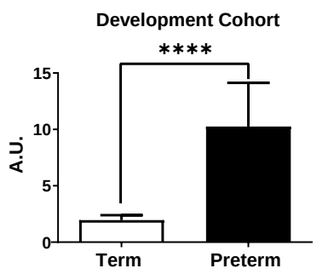
- Reflects the multi-etiological processes that occur during cervical remodeling
- Pre-clinical validation by *in vitro* cervical cell line studies and *in vivo* mouse model of preterm birth
- Combinatorial biomarker algorithm provides accurate prediction of preterm birth in asymptomatic women between 16 – 24 weeks of gestation

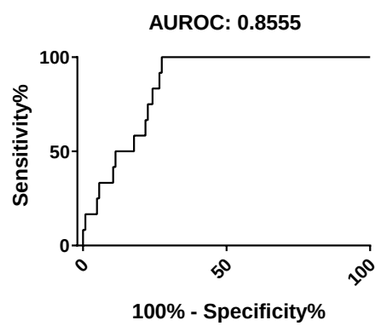
DEMOGRAPHICS OF STUDY COHORT

	Development		*Validation*	
	Term (N = 124)	Preterm (N = 12)	Term (N = 139)	Preterm (N = 10)
Maternal Age (Years)	33.42± 4.14	33.92 ± 3.47	33.07 ± 4.33	33.45 ± 3.56
Maternal BMI	25.09 ± 6.52	24.38 ± 5.43	25.11 ± 5.44	23.37 ± 4.84
Gravidity				
1	39 (31.5%)	1 (8.3%)	44 (31.7%)	2 (20.0%)
2 - 3	67 (54.0%)	6 (50.0%)	68 (48.9%)	6 (60.0%)
≥ 4	18 (14.5%)	5 (41.7%)	27 (19.4%)	2 (20.0%)
Parity				
Nulliparous	59 (47.6%)	3 (25.0%)	69 (49.6%)	2 (20.0%)
1	50 (40.3%)	5 (42.7%)	48 (34.5%)	5 (50.0%)
2 to 3	15 (12.1%)	4 (33.3%)	19 (13.7%)	2 (20.0%)
≥ 4	0 (0.0%)	0 (0.0%)	3 (2.2%)	1 (10.0%)
Singleton	124 (100.0%)	9 (90.0%)	138 (99.3%)	10 (100.0%)
Twins	0 (0.0%)	1 (10.0%)	1 (0.7%)	0 (0.0%)
Delivery Gestation (weeks)	39.23 ± 1.10	32.37 ± 4.18	39.37 ± 1.21	33.66 ± 3.14
Birth weight (grams)	3408 ± 448	1957 ± 751	3410 ± 487	2202 ± 651

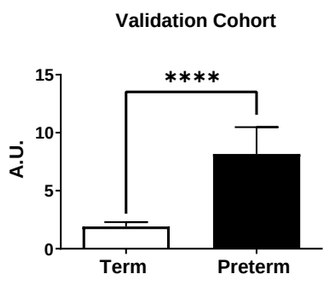
DIAGNOSTIC PERFORMANCE OF BIOMARKERS

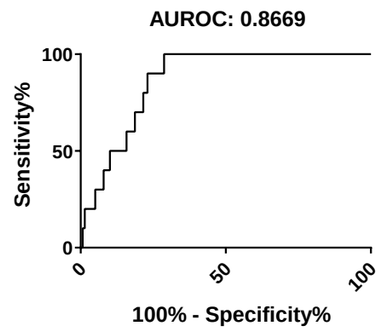
Development Cohort



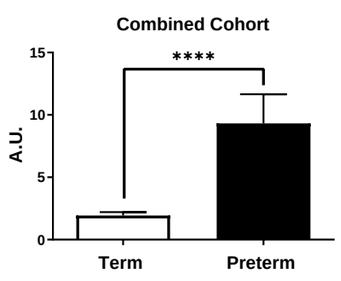


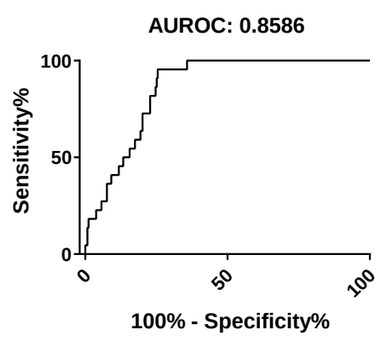
Validation Cohort





Combined Cohort





Diagnostic performance of the classifier

	Development	Validation	Combined
n	136	149	285
Sensitivity (%)	100.0 (75-100)	90.0 (60-99)	95.5 (78-100)
Specificity (%)	71.8 (63-79)	77.0 (69-83)	74.5 (69-79)
PPV (%)	25.5 (15-40)	22.0 (12-37)	23.9 (16-34)
NPV (%)	100.0 (96-100)	99.1 (95-100)	99.5 (97-100)
Likelihood ratio	3.543	3.909	3.747
P-value*	<0.0001	<0.0001	<0.0001

Values in parentheses are 95% confidence intervals. PPV: Positive predictive value; NPV: Negative predictive value. *Fisher's exact test

CONCLUSION

HIGH ACCURACY

The optimal multivariate model based on specific biological pathways, such as inflammation, hormonal and stress, produced mini biomarker panel tests. When combined, these achieved a sensitivity of 100% and specificity of 72% for the development cohort. This was confirmed in the validation cohort with a sensitivity of 90% and a specificity of 77%. Together, the combined cohort (development & validation) achieved a sensitivity of 96% and a specificity of 75%.

EARLY PREDICTION OF PRETERM BIRTH

These results once revalidated in a larger cohort, have the potential of generating a novel test that would predict preterm birth weeks or even months prior to any clinical presentation of PTB. Furthermore, the specific pathways represented by these biomarkers may suggest options for future preventative treatments for PTB.

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