Peripheral blood expression profiles act as biomarkers for postpartum depression in a high risk population

Mehta D [1], Kraus L [1], Rex-Haffner M [1], Newport J [2], Stowe Z [2, 3], Binder E [1, 2]

[1] Max Planck Institute of Psychiatry, Munich, Germany
[2] Emory University School of Medicine, Department of Psychiatry and Behavioral Sciences, Atlanta, GA, USA
[3] Emory University School of Medicine, Department of Obstetrics and Gynecology, Atlanta, GA, USA

Introduction

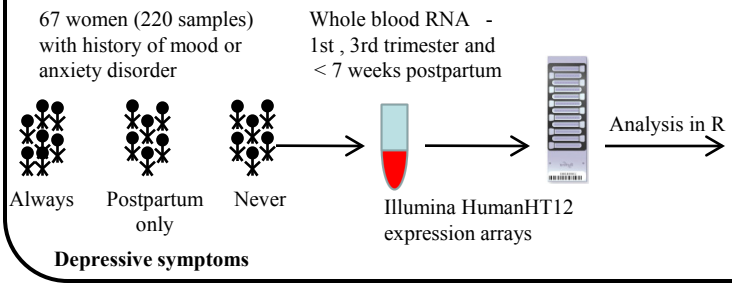
Postpartum depression affects approximately 13% of pregnant women and has a strong negative impact on maternal health and infant development. Early detection, possibly using biomarkers, coupled with timely treatment is therefore very important for the mother and the child. Despite the high prevalence and documented negative outcomes on both mother and the infant, the biological basis of postpartum depression (PPD) has not been adequately studied.

Depressive symptoms during pregnancy were associated with altered GR-sensitivity and GR-responsive peripheral blood gene expression in our recent study (Katz et al., 2011 submitted). In a previous study, no significant association between hormone levels and postpartum depression symptoms was observed, suggesting that sensitivity to changing hormone levels rather than hormone levels themselves might be associated with postpartum depression (Bloch, M. et al.,2000).

Aims of the study

The aim of this study was to identify biomarkers for postpartum depression by global assessment of peripheral blood gene expression changes during the peripartum period in a high risk cohort of pregnant women.

Experimental workflow



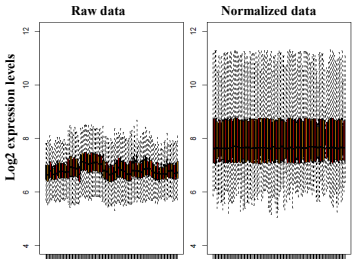


Figure 1a: **Box plots of gene expression data** – Box plots of gene expression intensities of 15,456 background-filtered probes before (left panel) and after vsn normalization (right panel) across all 220 samples on the X axis.

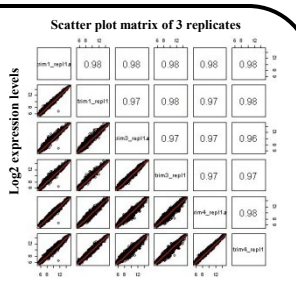


Figure 1b: **Replicates** – Scatter plots of technical replicates across the trimesters with Pearson correlations of 0.98-0.99 indicating high reproducibility of the expression data.

Results

Transcriptional profiles of >3,000 transcripts were significantly changed ($p < 3.7 \times 10^{-6}$) across pregnancy and early postpartum after Bonferroni multiple testing corrections (**Figure 2**).

116 transcripts were significantly differentially regulated between postpartum onset and never depressed groups and 43 transcripts were significantly differentially regulated between the always and never depressed groups in the 3rd trimester.

Expression levels of the 116 transcripts allowed to classify women with and without postpartum depression with an overall accuracy of 88%, 82.4% sensitivity and 93.3% specificity using two independent classification algorithms (**Figure 3**).

Significant overrepresentation of estrogen receptor transcription factor binding sites (ESR1) was observed only among the 116 transcripts significantly differentially expressed between the postpartum onset group and the non-depressed group of women. Several biological pathways were enriched (Table 1) within these 116 transcripts.

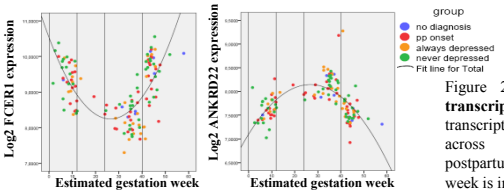


Figure 2: **Peripartum regulated transcripts** – Examples of transcripts significantly changed across pregnancy and early postpartum. Estimated gestational week is indicated on the X axis.

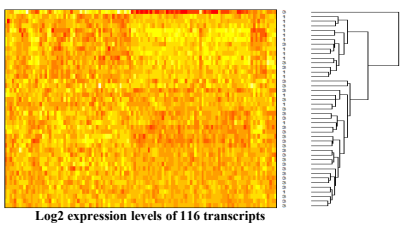


Figure 3: **Postpartum biomarkers** – Heat map of hierarchical clustering of 116 transcripts significantly regulated between postpartum onset depression and never depressed individuals in the 3rd pregnancy trimester. 3 indicates postpartum depression while 1 indicates never depressed individuals.

Pathways	Adjusted p-value of enrichment
Selenium	0.0083
Folic Acid Network	0.009
Adipogenesis	0.0105
Estrogen signalling	0.0246
Apoptosis	0.0252

Table 1: **Significantly enriched pathways** – Enrichment of transcripts belonging to biological pathways was assessed fro the 116 transcripts using the WebGestalt tool. P-values were adjusted for multiple testing correction.

Conclusions

Third trimester expression profiles of a subset of transcripts allowed highly accurate classification of women who developed postpartum onset depression, thus serving as potential biomarkers. Overrepresentation of ESR1 and estrogen signaling pathway fits to the previous hypothesis that differential sensitivity to changing steroid levels might be a vulnerability trait for postpartum depression. Our results suggest that postpartum depression risk may be biologically detectable as early as the third trimester, allowing timely prevention and treatment strategies.

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MPI of Psychiatry - Kraepelinstraße 2-10, 80804 Munich. Website - www.mpipsykl.mpg.de. Email - Divya Mehta: mehta@mpipsykl.mpg.de