Components of Mental Distress During Pregnancy in Relation to the Microbiome: Data from US and Swedish Cohorts

Mary Kimmel[1,2], Bangzhuo Tong[3], Alfons Edbom Devall[3,4], Richelle D. Björvang[1], Ina Schuppe-Koistinen[5,6], Lars Engstrand[5,6], Luisa W. Hugerth[3,5,6] Emma Fransson[1,5], Alkistis Skalkidou[1]

1. Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden
2. University of North Carolina
3. Department of Medical Biochemistry and Microbiology, Science for Life Laboratory, Uppsala University
4. Department of Molecular Biology, Umeå University, Umeå, Sweden
5. Centre for Translational Microbiome Research, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Stockholm, Sweden
6. Science for Life Laboratory, Karolinska Institutet, Stockholm, Sweden

Background: Mental distress in pregnancy is associated with negative long-term outcomes for mother and child. Yet, we have lacked biomarkers that could reflect the numerous physiologic and environmental changes happening across pregnancy that may indicate mental distress is putting parent and child at higher risk of negative outcomes. The gut microbiome may represent a proxy for environment, health behaviors, and host immune system functioning to better understand when distress requires intervention.

Methods: Second and third trimester pregnant individuals from the United States (n=83) and Sweden (n=429), completed the Edinburgh Postnatal Depression Scale (EPDS) and provided fecal samples analyzed with whole genome metagenomics. Measures of microbial community diversity (e.g., alpha-diversity and beta-diversity), the relative abundance of specific types of bacteria, and potential metabolomic functioning as assessed by Gut Brain Modules were analyzed in relation to different components of mental distress as assessed by the EPDS. In addition to the EPDS, individuals were characterized by past psychiatric history and diagnoses (e.g., Mini-international Neuropsychiatric Interview and the Structured Clinical Interview for DSM Disorders-V). Venn diagrams were used to assess which individuals were shared between clusters based on potential functioning and time point.

Results: Individuals from both cohorts with lower mental distress, assessed by the EPDS, had a significant change in alpha-diversity, as assessed by three different methods, from 2nd to 3rd trimester; while individuals with higher distress did not. Of note, distress of the US cohort differed significantly between 2nd and 3rd trimesters (p=0.016), while the Swedish cohort did not (p=0.65). Microbial communities of Swedish individuals differed based on higher or lower distress (p=0.015); only 3rd trimester US microbial communities trended toward being different (p=0.076). Differential abundance for individuals with higher distress included lower *Alistipes finegoldii* and *Clostridium aspargiforme. Bacteroides uniformis* was higher in individuals from the US who reported more past episodes of depression. Four distinct potential function groups were identified; varying in relation to higher anxiety, anhedonia, depression, or self-harm and by cortisol degradation, short chain fatty acid synthesis and degradation functioning. Cortisol degradation was lower in the Swedish cohort in clusters 2 and 3 in the 2nd trimester; cluster 2 associated with higher anxiety and cluster 3 with higher anhedonia. Lower cortisol degradation was associated with clusters 1 and 3 in the 3rd trimester; cluster 1 associated higher anhedonia and self-harm. In the US, cortisol degradation was lower in clusters 1 and 2 in the 2nd trimester and 3rd trimester; cluster 1 associated with self-harm in the 2nd trimester and higher anxiety in 3rd trimester. In Sweden, Cluster 2 in the 2nd trimester and Cluster 3 in the 3rd trimester had the highest number of shared individuals (n=71). In the US, Cluster 2 in both 2nd and 3rd trimester shared the most individuals (n=19).

Conclusions: It is important to consider subtypes of symptoms, especially as anxiety, anhedonia, depression and self-harm help better group individuals in relation to microbiome compositions and potential functioning. Pregnant individuals with greater mental distress may have a less adaptable microbiome. It has generally been thought that the 2nd trimester is a period of lower mental distress both due to more stability of both physiologic and psychologic changes; and yet this research indicates there are subsets of individuals with higher distress in the 2nd trimester reflected by microbial functioning. This study also supported prior studies implicating bacteria related to dietary fiber, particularly for individuals with a longer lifetime history of mental distress. It is a complex picture that is emerging between symptom subtypes, timing, and microbiome potential functioning; but also, a picture that indicates there is the potential to combine these three considerations.