Epigenetic regulation of placenta *NR3C1*: Mechanism underlying the impact of prenatal marijuana on infant development?

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Background: The social acceptability and political landscape of marijuana as well as its potency have changed dramatically in the last two decades, leading to increased use by pregnant women and increased fetal exposure to cannabinoids. Yet, little is known regarding the impact of "modern potency" prenatal marijuana exposure on offspring neurodevelopment or mechanistic pathways. We propose that prenatal marijuana exposure will alter epigenetic regulation of placenta glucocorticoid signaling (indicated by *NR3C1* methylation) leading to infant neurobehavioral and neuroendocrine dysregulation.

Methods: Participants were 153 mother-infant pairs from a low-income, diverse sample (M_{age} =26±6). Marijuana and tobacco use were assessed using Timeline Followback methodology with biochemical confirmation (THC, nicotine, carbon monoxide). Newborn neurobehavior was assessed at seven time points over the first postnatal month using behavioral and saliva cortisol response to the NICU Network Neurobehavioral Scale (NNNS). Methylation of placental *NR3C1* promoter exon 1F was assessed using bisulfite pyrosequencing in a subsample.

Results: Preliminary analyses revealed increased signs of withdrawal, altered self-regulation, and decreased orientation to stimuli (p's=.02-.08) and altered cortisol regulation (p's=.04-.09) over the first postnatal month in marijuana-exposed vs tobacco-exposed and control infants. We also found preliminary evidence for dose response associations between total marijuana use over pregnancy and signs of withdrawal and altered self-regulation (*p*'s<.05). Methylation of *NR3C1* was altered in marijuana-exposed vs comparison offspring (*p*s=.03-.12); total prenatal marijuana use was also associated with *NR3C1* methylation (*p*s<.05). Finally, *NR3C1* methylation was associated with infant self-regulation, attention, and lethargy (*p*s<.05) and infant cortisol response.

Conclusions: Results highlight the impact of prenatal marijuana exposure on early neurobehavioral and neuroendocrine dysregulation. Although this study is preliminary with a focus on one glucocorticoid signaling gene, interrogating the placenta methylome may serve as a novel approach to elucidate biomarkers of exposure and mechanistic pathways underlying the impact of prenatal marijuana on offspring neurodevelopment.