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## Prenatal Cannabis Exposure and Neurodevelopmental Gene Up-regulation: Longitudinal Impact on Childhood Cortisol Levels

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Cannabis use among pregnant individuals is rising, though prevalence estimates vary from 2% to 36% depending on detection methods and populations studied. Prenatal cannabis exposure (PCE) can have substantial effects on a child's development and stress reactivity, with exposed children showing higher hair cortisol levels. It is also known to impact the expression of placental genes regulating neurotransmission and neuronal structures involved in stress response systems. We hypothesized that PCE would alter neurodevelopmental gene expression, leading to elevated cortisol levels in childhood.

Factor analysis of placental gene expression among genes known to regulate neurodevelopment identified two gene clusters from 329 mother-child dyads: cluster A (FOXP1, SRD5A3, and ZNHIT6; reliability=.70) and cluster B (MAOA, CDKL5, ZNF507, and MECP2; reliability=.79). Expression levels for the two clusters were dichotomized at the median. Logistic regression analysis demonstrated that PCE was associated with higher expression in both cluster A (odds ratio, or OR=2.164, p=.022) and cluster B (OR=2.050, p=.032). Logistic regression was followed by generalized estimating equations on a subset (n=68) that incorporated intra-individual changes over time, revealing that high expression of each cluster was associated with elevated cortisol levels (p=.015, .016) through ages 2-5.

These findings suggest long-term impacts of cannabis use on stress regulation and align with evidence linking PCE to heightened stress sensitivity during childhood. As cannabis use continues to rise, targeted public health interventions are critical to inform pregnant individuals of potential neurodevelopmental consequences in their offspring.