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# Susceptibility to Substance Use Initiation: The Developmental Cascade From Placental HPA-Axis Programming to Infant Temperament

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The placenta plays a critical role in regulating fetal glucocorticoid exposure and ultimately infant neurodevelopment. Understanding the association of HPA-axis gene expression with child temperament is crucial as emotional dysregulation and heightened reward sensitivity have been linked to increased susceptibility for early substance use initiation. This study analyzed HPA-axis gene expression in placental tissues collected at birth from a subsample of 219 mother-child dyads. Factor analysis identified two distinct gene clusters associated with HPA-axis functioning. The first factor (reliability=0.72) comprised 11β-HSD2, NR3C1, and DYRK1A, while the second factor (reliability=0.87) included CFL1, NCOR1, and NR3C1. The associations between these HPA-axis-related placenta gene clusters and infant temperament were assessed longitudinally at five timepoints between 6 and 36 months of age, with analyses stratified by child sex. We hypothesized that both factors would be associated with emotional difficulties and that boys would be more vulnerable to in-utero HPA-axis dysregulation. Lower expression of HPA factor 1 genes significantly reduced high intensity pleasure (p=.044) in both sexes and effortful control (p=.014) in males only. Lower expression of the HPA factor 2 genes was associated with decreased effortful control (p=.024) and increased sadness (p=.034) in both sexes, while decreased effortful control (p=.010) and increased negative affectivity (p=.014) was observed in males only. Results demonstrated the relationship between HPA-axis regulation and sensation-seeking temperaments, underscoring the importance of placental HPA-axis functioning as a potential early life marker for later substance use vulnerability. Males with lower HPA-axis gene expression may have temperaments more susceptible to early substance use.