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The role of sex and inflammation on the developing brain in neonatal abstinence syndrome (NAS)

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Male infants exposed prenatally to opioids are more likely to develop withdrawal signs (NAS), require pharmacotherapy (NAS-Tx) and have longer hospitalizations compared to females. Emerging animal data show that opioids exert sex-dependent inflammatory effects through non-neuronal pathways. Opioid binding to TLR4 on glial cells stimulates inflammatory mediator release and brain injury, reinforcing reward/addictive behavior with deleterious effects on cognition. We aim to understand a potential sex-specific impact of prenatal opioid exposure on pro-inflammatory pathways and the developing brain using neonatal saliva and magnetic resonance imaging (MRI). Saliva samples were collected within 48 hours of birth from neonates with NAS (n=16) and non-opioid exposed infants (sex- and age-matched controls; n=16). Samples underwent transcriptomic analyses for pro-inflammatory (*IL1B, IL6, TNFα, CXCL1, MCP1),* anti-inflammatory (*IL10*), and key reward-signaling (*DRD2*) genes. Compared to controls, neonates with NAS had 3-fold higher expression of *IL6* and *MCP1,* with even higher expression (5-fold) in NAS-Tx ($p \leq 0.05$). Females with NAS-Tx had 4-fold higher expression of *IL1B, IL6, MCP1,* and downregulation (<1-fold expression) of *IL10* than males ($p \leq 0.05$); the expression of *IL6* and *MCP1* correlated with *DRD2 (*$r=0.99$, $p<0.05$). White matter hyperintensity was seen in four of five females with NAS, one male with NAS had a normal MRI. All controls had a normal MRI. Functional MRI is ongoing. Prenatal opioids may promote inflammation and reinforce reward properties, with a greater effect in females than in males. Whether inflammation contributes to the severity of NAS and white matter abnormalities in females remains subject to further research in larger cohorts.