Pediatric RESEARCH

COMMENT

Commentary on salivary cortisol levels as a biomarker for severity of withdrawal in opioid-exposed newborns

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In this month's issue of *Pediatric Research*, Rodriguez et al.[1] aimed at evaluating salivary cortisol as a biomarker of the severity of withdrawal in newborns exposed to prenatal opioids. Over the past several years, studies have focused on predictors that enable practitioners to stratify infants with neonatal opioid withdrawal syndrome (NOWS) into low-, medium-, and high-risk profiles. Various perinatal risk factors have been incorporated into assessment models to forecast the severity of withdrawal mandating pharmacotherapy, length and dosage of pharmacological treatment, and duration of hospital stay.[2,3] Lately, promising genomic variants were incorporated in the risk stratification of infants with prenatal opioid exposure. Although the costs of genetic sequencing are consistently trending down, large sample sizes are required for valid computational approaches.[4] In the meanwhile, prenatal, demographic, and clinical determinants remain the most available bedside tools used in the prognostication of the severity of withdrawal.

The authors demonstrated an association of high salivary cortisol in opioid-exposed newborns with severe withdrawal symptoms requiring pharmacological treatment. They analyzed salivary cortisol levels (SCLs) in 22 infants ≥37 weeks' gestation with reliable salivary samples in the first week of life. Half of the study infants required pharmacological treatment for severe withdrawal. They found that SCLs during the first week of life were twofold higher in infants who subsequently received pharmacotherapy compared to the same at risk of withdrawal infants who did not require pharmacological treatment, $P = 0.003$. Further, excluding the first 72 h of life, where SCLs could be elevated secondary to the stress of parturition, the SCLs (9 samples) were persistently higher in infants >72 h of life who needed subsequent treatment, with a median of 1.47 µg/dl, compared to a median of 0.58 µg/dl in infants discharged home without pharmacological treatment (22 salivary samples).[1]

The results were significant; however, the number of reliable samples in the study was not large enough to draw inference. The authors realistically addressed the limitations of the small sample size, as well as the challenges in detecting reliable cortisol levels because of inadequate aliquots in 70% of the collected samples. Of note is an important observation to be gained for future applications was that the post hoc pairwise comparisons of five buccal swab collection intervals showed a significant increase in collection rate with >10-min collection duration.

The authors attributed the findings of sustained high SCLs to the underlying autonomic dysregulation of the severely withdrawing infants requiring subsequent treatment.[1] The altered capacity of the hypothalamic–pituitary axis (HPA) to maintain homeostasis in response to stress and opioid exposure could result in overstimulation of cortisol release. In contrast, differences in SCLs were not demonstrated with other prenatal substance exposures; for example, there were no differences in SCLs in infants exposed to prenatal cocaine compared to non-exposed infants at discharge.[5]

In a recent study of 70 newborns exposed to prenatal opioids, the withdrawal scores of the infants were compared to their mothers' hair cortisol levels. Maternal hair cortisol reflects cortisol release in the 3 months prior to delivery time. The severity of withdrawal of infants (indexed by prolonged length of hospital stay and treatment days) was associated with lower cortisol levels in maternal hair within 72 h of delivery.[6] The findings contradicting the authors' hypothesis were explained by the possible blunting of the cortisol response secondary to suppression of the HPA, which occurs with chronic exposure to maternal stress and opioid use.[7]

The authors highlighted a significant correlation concerning the persistence of elevated SCLs beyond the first 72 h of life as a stress biomarker for the need to receive pharmacological treatment.[1] A correlation made in retrospect. This postnatal period is characterized by a physiologic surge in cortisol in infants mirroring the high cortisol levels in mothers secondary to the stress of labor. It coincides with the time interval where prenatally opioid exposed infants start to show signs of withdrawal and initiation of pharmacotherapy if indicated by withdrawal scores. Therefore, SCLs could be of limited prediction in NOWS requiring pharmacotherapy within 72 h of birth. In future studies, it is plausible to include testing of both maternal and infant hair cortisol levels as chronic stress biomarkers, in addition to salivary cortisol as an index of acute stress in newborns. The combination would yield a better understanding of the pathophysiology of cortisol release and its significance as a prognostic tool for outcomes in infants exposed to prenatal opioids.

While accounting for known perinatal and demographic risk factors such as gender, gestational age, birth weight, maternal rehabilitation opioids, other substance exposure, tobacco, and type of feeding,[2,6] the authors found that larger birth weight and exposure to prenatal buprenorphine were associated with the need for treatment.[1] Another characteristic of evolving significance is ethnicity/race. White race was associated with significantly higher use of pharmacological treatment compared to black race,[8] which is in congruence with the identified differences in race/ethnic allele frequencies and associated single-nucleotide polymorphisms in the opioid receptors in neonates with NOWS.[4]

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Not to go unnoticed, the mother–infant dyad interaction is a major determinant in the modification of stress response and should be a measured variable in studies evaluating cortisol levels. Particularly, in infants at risk of opioid withdrawal, the sustained physical contact is a significant modifier of their disorganized and self-dysregulated state.[9] The mother–infant interactions, such as skin-to-skin contact, and non-pharmacological containment techniques provided by caregivers, i.e., consoling/cuddling and massaging, are known to influence stress response via the HPA.

Rooming-in and continuous skin-to-skin care (kangaroo) increase concordance between infants and their mothers' SCLs.[10] Furthermore, the duration of rooming-in was shown to influence salivary cortisol, for instance, full-day rooming-in for 24 h versus partial (14 h) maternal stay improved breastfeeding and reduced newborn stress reactivity as shown by lower SCLs.[11] Relevantly, infants who received simultaneous multisensory auditory, tactile, visual, and vestibular (rocking) intervention by caregivers demonstrated a significant steady decline in salivary cortisol compared to those receiving no intervention or only tactile stimulation.[12] It is challenging to disentangle where the net stress-protective factors in infants who do not require pharmacological treatment might be marked, i.e., lower burden of prenatal opioids; less polysubstance exposure; specific demographic influences; early non-pharmacological interventions; innate metabolic, genetic, and epigenetic profiles; or a combination of various elements.

Moreover, salivary cortisol could also become a potential biomarker for long-term neurobehavioral outcomes. Previous studies have shown that prolonged mother–infant separation after delivery increases negative long-term consequences of preterm and term infants.[13] The hyperactivity of the HPA with sustained elevated salivary cortisol is associated with cognitive impairment and disruptive behaviors that may be related to destructive changes in the hippocampus.[14,15]

The collective findings in the study demonstrate feasibility of the use of salivary cortisol as a possible biomarker for risk stratification in infants exposed to prenatal opioids. In addition, it highlights other areas that warrant further investigation, such as the loss of cortisol circadian rhythm and evaluation of continuous monitoring of SCLs during prolonged pharmacological treatment.

The Food and Drug Administration–National Institutes of Health Joint Leadership developed the BEST (Biomarkers, EndpointS, and other Tools) to clarify distinctions between clinical assessments and prognostic biomarkers, which is defined as observational data regularly used to identify patients more likely to have a particular outcome.[16] Moving forward, it is strongly recommended to study and validate promising biomarkers—in particular non-invasive tools—for the prediction and prognostication of the severity of withdrawal and long-term neurobehavioral outcomes in childhood and adolescence.

ADDITIONAL INFORMATION

Competing interests: The author declares no competing interests.

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