

Fetal Opioid Exposure and Smaller Birth Head Circumference: Cause for Concern?

Mark L. Hudak, MD, Kartikeya Makker, MD

On a daily basis, the media remind us that our national opioid crisis unrelentingly causes human tragedy. Rates of opioid prescriptions, admissions to substance use disorder treatment programs for the misuse of prescription drugs, and opioid-related deaths have all increased significantly over the past decade.¹ The Centers for Disease Control and Prevention estimates that opioid overdose contributed to 140 077 emergency department visits and 78 840 acute hospitalizations in 2015 and to 42 249 deaths in 2016 (669 in children age ≤19).² Now, more people die in the United States of opioid overdose than of motor vehicle trauma. The striking increase in the death rate from all drug overdoses (from slightly >6 per 100 000 in the population in 1999 to 19.8 per 100 000 in the population in 2016) has resulted from sequential increases in deaths associated with prescription opioids (circa 2000), a resurgence of heroin-related fatalities (circa 2010), and a recent steep climb in the mortal abuse of potent synthetic opioids (circa 2013). The largest and most visible impact on children stems from the increased use of opioids by women of child-bearing age. The number of newborns with neonatal abstinence syndrome (NAS) has exploded because the rate of this condition has risen fivefold since 2000. In some states, >30 infants per 1000 live births develop NAS, effectively transforming some NICUs into NAS wards.³

Although NAS can be a challenging condition to manage and requires intense investment of human resources, acute signs of withdrawal are transient and ultimately resolve. More important than how to manage NAS are these 2 questions: What are the best methods to prevent NAS? What, if any, are the long-term effects of fetal and neonatal opioid exposure on the developing child?

Primary prevention of NAS entails either reducing the number of pregnant women on opioids or minimizing the number of women on opioids who become pregnant. Physician education about the harmful effects of opioids, better prescription drug-monitoring programs, and new state regulations about opioid prescriptions promise to bear fruit in reducing the number of pregnant women who will use prescription opioids. Similarly, expanded availability of long-acting reversible contraception will more effectively forestall unplanned pregnancies in women who are fertile and on opioids. Parenthetically, we must note that not all women on opioid maintenance therapy misused or abused opioids. Well-intentioned but imperfect physician prescription of opioids for legitimate medical reasons may lead to opioid dependency. One in 300 mothers undergoing cesarean delivery becomes dependent on opioids as a consequence of postoperative pain management.

Inevitably, there will still be infants born with NAS. How opioid exposure

Division of Neonatology, Department of Pediatrics, College of Medicine – Jacksonville, University of Florida, Jacksonville, Florida

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Address correspondence to Mark L. Hudak, MD, Department of Pediatrics, College of Medicine – Jacksonville, University of Florida, 653-1 W 8th St, LRC Box L-1600, Jacksonville, FL 32209. E-mail: mark.hudak@jax.ufl.edu

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will affect these children as they develop remains more than a bit murky. Most infants with NAS sustain fetal coexposure to other drugs or substances (including cigarette smoke, marijuana, benzodiazepines, and cocaine), and many will mature in environments rich with adverse social determinants of health. This complex battery of confounders has always challenged researchers who have sought to disentangle opioid-specific effects. Although it is clear that some infants with NAS attain normal neurodevelopmental outcomes as children, there is also growing concern that opioid exposure is associated with higher rates of attention-deficit/hyperactivity disorder, abnormal externalizing behaviors, and poorer executive function.

In this issue of *Pediatrics*, Towers et al⁴ detail the results of a large prospective cohort study in a single institution that aimed to determine if antenatal opioid exposure independently reduced head circumference (and by inference, brain volume⁵) at birth. In this trial, the investigators compared infants born at ≥ 34 weeks' gestation to mothers on opioids who subsequently received pharmacologic treatment of NAS with contemporaneous control infants without NAS matched for gestational age (± 4 days), race, parity, and mode of delivery. Although a previous investigation from this center and other reports had suggested an association between antenatal opioid exposure and reduced head circumference, an inconsistent assessment of gestational age, imperfect confidence about the lack of exposure in controls, and imprecision due to the possible confounding effect of other drug coexposures prevented a secure inference. Strengths of the current study include universal dating of pregnancies by early ultrasound, multiple antenatal maternal urine

drug tests for exposures in both cases and controls, and the use of a fairly robust statistical methodology to account for confounding exposures.

Compared with well-matched controls, newborns with NAS demonstrated a highly significant (nearly 1 cm) decrease in the mean head circumference. The primary outcome, a head circumference at or below the 10th percentile, occurred in 30.1% of newborns with NAS versus 11.9% of controls. Although a univariate analysis revealed that infants with NAS were more likely to have had several other coexposures, only benzodiazepines and marijuana were independent risk factors for NAS in addition to opioids. Neither of these exposures, however, was a significant independent risk factor for the primary outcome. Another finding was that newborns with NAS showed proportionately greater decreases in head circumference than in birth weight. This was unlikely to have been mediated by uteroplacental insufficiency or nutritional deficiencies because these conditions produce asymmetric growth that disrupts fetal weight gain to a greater extent than head circumference. Hence, an alternative hypothesis that opioids exert a direct effect on head growth (and by implication, on brain growth) becomes more attractive. Even more compellingly, the overall distribution of the standardized head circumference measures for newborns with NAS was shifted to the left. Might that suggest that opioid exposure will decrease the likelihood for every newborn with NAS to reach his or her genetic potential for brain growth and development by adulthood? Some evidence does point to long-term reductions in regional brain volumes, and basal ganglia involved in neurotransmission may be particularly affected.^{6,7} There is cause to be concerned about smaller head circumferences at birth in a population. Evidence from

a multigenerational birth cohort study in Sweden links smaller head circumference at birth in normal children with poorer school performance and lower occupational achievement in adulthood.⁸ It would be remiss not to note in this context that fetal exposure to alcohol, which impairs brain growth as a function both of timing and of cumulative dose, is the single largest and preventable cause of intellectual deficit in childhood.

Some other questions now become important. If fetal opioid exposure reduces brain growth and affects long-term neurodevelopment, are these outcomes mediated by exposure during a critical window, or is the effect cumulative over a longer time frame (during neurogenesis, neuronal migration and differentiation, or synaptogenesis)? To what extent are the effects dose related? Are fetuses with lower or more abbreviated exposures at a lesser risk for reduced head and brain growth? Unfortunately, our ability to quantify the dose and duration of every drug used by women who are pregnant and on opioids (including opioids) is exceedingly limited in routine clinical practice. Some answers may derive from an ongoing prospective cohort study that these investigators are conducting on newborns with lower or truncated fetal exposure to opioids who did not develop NAS. Additional evidence revealing that the reduction of maternal opioid use can protect normal fetal head and brain growth should energize discussion about refining the management of the opioid-maintained maternal-fetal dyad, with the goal not solely to prevent NAS but more importantly to optimize the outcome of the child.

ABBREVIATION

NAS: neonatal abstinence syndrome

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