EDITOR’S NOTE: Studies for this issue were identified using alerts from Archives of Disease in Childhood-Education and Practice, Archives of Disease in Childhood-Fetal and Neonatal, Archives of Disease in Childhood, British Medical Journal, Journal of the American Medical Association, New England Journal of Medicine, Pediatric Infectious Disease Journal, Pediatrics, The Journal of Pediatrics, and The Lancet. Search terms were “paediatrics” [All Fields] OR “pediatrics” [All Fields] OR “pediatrics” [MeSH Terms]. Cleo Pappas, MLIS, Library of the Health Sciences, University of Illinois at Chicago, contributed to the review and selection of this month’s abstracts.

—Jordan Hupert, MD

EVIDENCE-BASED MEDICINE PEARL: ODDS RATIO (OR): The OR often is used in studies measuring risk of an outcome given a specific exposure. The odds of an outcome occurring is the ratio of the probability of the outcome occurring divided by the probability of the outcome not occurring. Mathematically, this is $p/(1-p)$, where $p$ is the probability. The OR is the odds of an outcome occurring in the exposed population divided by the odds of the same outcome occurring in the unexposed population—a measure of association. The OR may be used in many types of studies, but perhaps is most used in case-control studies. For example, in a case-control study evaluating the association of childhood migraines with a history of infantile colic, 72.6% of children with migraines and 26.5% of children without migraines had a history of infantile colic. The OR is $\left(\frac{72.6\%}{26.5\%}\right) / \left(\frac{27.4\%}{73.5}\right) = 7.35$. This is known as the crude OR. The aOR (adjusted by a computer for possible confounders such as gestational age, colic in first-degree relatives, etc) listed in the case-control study by Romanello et al, is 6.61 (95% CI 4.38-10.00). Thus, patients with childhood migraines were 6.61 times more likely to have a history of infantile colic than patients without childhood migraines. This association is statistically significant, as the 95% CI does not cross 1 (see the Romanello et al; JAMA 2013;309:1607-12).

—Jordan Hupert, MD

EVIDENCE-BASED MEDICINE LIBRARIAN PEARL: “PEARL CULTURING”: Five valuable techniques may increase the number of relevant articles retrieved on a desired topic using those articles already retrieved: (1) In PubMed, after finding applicable articles either by a search or by Single Citation Matcher, select related citations; (2) In PubMed, change the view of applicable articles from summary or abstract to Medline. Then look for medical subject headings (MeSH terms) that have been assigned to the applicable article. Perform a search with those terms; (3) Look for other articles written by the authors of applicable articles; (4) Plug applicable articles into Web of Science to determine references cited and citing articles of applicable articles; and (5) Plug applicable articles into Google Scholar to determine citing articles. These techniques are particularly useful for topics that have not been extensively studied.

—Cleo Pappas, MLIS

Childhood migraine is associated with a history of infantile colic

Question Among otherwise healthy infants, what is the association of infantile colic with later development of childhood migraine headaches?

Design Case-control study.

Setting 3 European tertiary care hospitals (Robert Debré, Paris, France; Sacco, Milan, Italy; and Santa Mariadella Misericordia, Udine, Italy).

Participants Consecutive children presenting to the emergency department, 6-18 years old, who were diagnosed with primary headaches by a pediatric neurologist. Control participants were children in the same age range who visited the emergency department of each participating center for minor trauma.

Intervention Childhood migraine headache.

Outcomes The primary outcome was the difference in the prevalence of infantile colic between children with and without a diagnosis of migraine.

Main Results Children with migraine were more likely to have experienced infantile colic than those without migraine, (72.6% vs 26.5%; OR, 6.61, 95% CI 4.38-10.00, $P < .001$) either migraine without aura ($n = 142$; 73.9% vs 26.5%; OR, 7.01, 95% CI 4.43-11.09, $P < .001$), or migraine with aura ($n = 66$; 69.7% vs 26.5%; OR, 5.73; 95% CI 3.07-10.73, $P < .001$). This association was not found for children with tension-type headache (35% vs 26.5%; OR, 1.46, 95% CI 0.92-2.32; $P = .10$).

Conclusions The presence of migraine in children and adolescents aged 6 to 18 years was associated with a history of infantile colic.

Commentary Infantile colic is a common and distressing disorder of early infancy characterized by excessive and often inconsolable crying in an otherwise healthy infant. The infants often are assumed to be experiencing abdominal pain, despite no direct evidence for this localization. Moreover,
therapies aimed at reducing intestinal gas or altering the infants’ diet have been largely unsuccessful. The study by Romanello et al is a case-control study that demonstrates that children with migraine headaches are more likely to have had colic as infants. Further bolstering the evidence for children with migraine headaches are more likely to have an infant with colic. Infants with migraines are more sensitive to stimuli, both during and often between attacks. It is possible that infant colic is an early life manifestation of those genes that later in life are expressed as migraine headache. Infants with colic may be more sensitive to the stimuli they encounter in the first weeks of life as their sensory processing abilities rapidly develop, and may express this sensitivity through excessive crying. Prospective longitudinal infant cohort studies are needed to rigorously examine this association. If infant colic is a migraine-related disorder, there are major treatment implications. Behavioral therapies, such as limiting certain types of stimulation, or pharmacologic migraine therapies known to be safe in early infancy, such as acetaminophen, could be studied.

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References


Thin catheter surfactant administration during spontaneous breathing in very low birth weight infants is associated with reduced need for mechanical ventilation

Question Among very low birth weight infants, what is the therapeutic efficacy of thin catheter administration of surfactant during spontaneous breathing, compared with surfactant administration via endotracheal intubation (and then extubation), on the rates of early mechanical ventilation and the development of bronchopulmonary dysplasia (BPD)?

Design Randomized, controlled trial.

Setting Neonatal intensive care unit of Zekai Tahir Burak Maternity Teaching Hospital, Ankara, Turkey.

Participants Inborn preterm infants with gestational age < 32 weeks with respiratory distress syndrome (RDS).

Intervention Thin catheter surfactant administration during spontaneous breathing versus the endotracheal tube intubation/ventilation/extubation technique for administration of surfactant.

Outcomes Primary outcome: mechanical ventilation within the first 72 hours after birth. Secondary outcomes: duration of nasal continuous positive airway pressure (CPAP), duration of mechanical ventilation, and development of BPD.

Main Results Mechanical ventilation in the first 72 hours of life was significantly lower in the thin catheter group compared with the endotracheal tube group (30% vs 45%, number needed to treat = 7, 95% CI 4-58). Mean duration of both nasal CPAP and mechanical ventilation were significantly reduced in the thin catheter group (78 hours vs 116 hours P < .006 and 35.6 hours vs 64.1 hours P < .002, respectively). The BPD rate was marginally statistically lower among infants treated with the thin catheter technique (absolute risk reduction 9.9%, 95% CI 0.03-19.8%; number needed to treat = 11, 95% CI 6-3339).

Conclusions The thin catheter technique significantly reduces the need for and duration of mechanical ventilation, as well as the BPD rate in very low birth weight infants.

Commentary Recent trials (COIN, SUPPORT) have demonstrated that aggressive continuous positive airway pressure can prevent BPD in the highest risk neonates. Unfortunately, 50%-80% of infants in these trials eventually required intubation. These findings have led to renewed interest in less invasive ways to administer surfactant in order to prevent prolonged intubation and mechanical ventilation. Kanmaz et al have developed a technique to deliver surfactant quickly and safely without the use of forceps, utilizing a small-bore catheter in spontaneously breathing infants <32 weeks gestational age with signs and symptoms of RDS. This technique resulted in a lower rate of mechanical ventilation and less BPD when compared with infants treated with endotracheal intubation administration of surfactant. Kanmaz et al should be applauded for their ingenuity in attempting to administer surfactant in the most physiologic, least invasive way possible. Whether this protocol will provide benefit over the endotracheal method when applied at other centers by different operators remains to be demonstrated. Another interesting question is whether this technique would provide additional benefits beyond endotracheal surfactant administration if performed prophylactically, prior to the development of RDS.

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Prenatal valproate exposure is associated with autism spectrum disorder and childhood autism


Question Controlling for known risk factors, what is the association of prenatal valproate exposure with development of autism spectrum disorder or childhood autism, compared with unexposed children?

Design Prospective, population-based birth cohort study.

Setting Denmark.


Intervention Prenatal valproate.

Outcomes Autism spectrum disorder and childhood autism.

Main Results Of 655 615 children born from 1996 through 2006, 5437 were identified with autism spectrum disorder, including 2067 with childhood autism. The mean age of the children at end of follow-up was 8.84 years (range, 4-14; median, 8.85). The estimated absolute risk after 14 years of follow-up was 1.53% (95% CI, 1.47%-1.58%) for autism spectrum disorder and 0.48% (95% CI, 0.46%-0.51%) for childhood autism. Overall, the 508 children exposed to valproate had an absolute risk of 4.42% (95% CI, 2.59%-7.46%) for autism spectrum disorder, adjusted hazard ratio (HR), 2.9 (95% CI, 1.7-4.9) and an absolute risk of 2.50% (95% CI, 1.30%-4.81%) for childhood autism, adjusted HR, 5.2 (95% CI, 2.7-10.0). When restricting the cohort to the 6584 children born to women with epilepsy, the absolute risk of autism spectrum disorder was 2.95% (95% CI, 1.42%-6.11%), adjusted HR, 2.9 (95% CI, 1.4-6.0) vs 2.44% (95% CI, 1.88%-3.16%) for autism spectrum disorder and 1.02% (95% CI, 0.70%-1.49%) for childhood autism among 6152 children not exposed to valproate.

Conclusions Maternal use of valproate during pregnancy was associated with a significantly increased risk of autism spectrum disorder and childhood autism in the offspring, even after adjusting for maternal epilepsy. For women of childbearing potential who use antiepileptic medications, these findings must be balanced against the treatment benefits for women who require valproate for epilepsy control.

Commentary Christensen et al present strong evidence that fetal valproate exposure is associated with increased risks of autism and autism spectrum disorder. Study strengths include the large population-based cohort, extended longitudinal follow-up, very few subjects lost to follow-up, and analyses adjusting for many potentially confounding factors. Limitations include inadequate information on folate, alcohol or illicit drugs use, no adjustments for other prescribed drugs, and lack of measures for medication compliance or valproate blood levels. In addition to autism risk, fetal valproate exposure has been associated with a number of specific congenital malformations, and with cognitive impairment even in the absence of malformations. Fetal valproate exposure is also associated with reduced IQ (7-10 points) compared with other antiepileptic drugs, and exhibits dose-dependent adverse effects across a range of cognitive domains. Valproate is commonly used in women of childbearing age for seizures, pain, and psychiatric disorders. Given the established risks of fetal valproate exposure, clinicians should inquire about possible fetal valproate exposure in children with cognitive or behavioral problems, including autism. Clinicians should carefully screen children with a history of fetal valporate exposure for anatomical defects and neuropsychologic impairments in order to detect abnormalities and institute appropriate interventions.

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References

Setting Dunedin, New Zealand.


Intervention Television viewing.

Outcomes Criminal convictions, violent convictions, diagnosis of antisocial personality disorder, and aggressive personality traits in early adulthood.

Main Results After controlling for sex, IQ, socioeconomic status, previous antisocial behavior, and parental control, young adults who had spent more time watching television during childhood and adolescence were significantly more likely to have a criminal conviction, OR 1.27 (95% CI 1.00-1.61), a diagnosis of antisocial personality disorder, OR 1.61 (95% CI 1.10-2.36), and more aggressive personality traits (statistically significant linear regression coefficient) compared with those who viewed less television (results represent the outcome associated with a 1-hour increase in weekday television viewing). The associations were similar for both sexes, indicating that the relationship between television viewing and antisocial behavior is similar for male and female viewers.

Conclusions Excessive television viewing in childhood and adolescence is associated with increased antisocial behavior in early adulthood.

Commentary There is no argument that watching television can have negative effects on children. It is correlated with overweight, problems with executive function and attention, aggressive behavior, and early initiation of sex. This study takes the alarm to a new level, reporting not just a correlation between television viewing and antisocial personality disorder, but that every extra hour of television watched by children on a weeknight increased by 30% the risk of a criminal conviction by age 26 years. The authors controlled for socioeconomic status, sex, IQ and parental control. The results suggest that television viewing is very dangerous for our youth. However, the study has some notable limitations. It is based on recall, so the actual number of hours may or may not be accurate. Second, there is no data on the content of the programming they watched. Current evidence suggests that the content of the programming is as important – and likely more important – than the amount of time spent watching the programming. Third, it is entirely possible that excessive television viewing is a symptom rather than a cause of antisocial behavior, and conversely, that the activities that might keep children away from the television are protective against antisocial behavior. Fourth, parental control is only one aspect of parenting and family culture, both of which are strong contributors to behavioral outcomes. The study is interesting and warrants attention, but the effects of television on children are more nuanced than the study suggests.

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References


Prenatal cocaine exposure is associated with variable, small effects on adolescent functioning


Question Compared with unexposed adolescents, what is the association of prenatal cocaine exposure with adolescent function (behavior, cognition/school outcomes, physiologic responses, and brain morphology and functioning)?

Design Systematic review. Criteria for study inclusion were nonexposed comparison group, human adolescents aged 11 to 19 years, peer-reviewed, English-language, and adolescent outcomes.

Setting Largely urban with one study set in a rural area.

Participants Low income, age 11-17 years, predominantly African American.

Intervention Prenatal cocaine exposure.

Outcomes Measures of behavior, cognition/school performance, brain structure/function, and physiologic response.

Main Results 27 studies representing 9 cohorts met inclusion criteria. 11 examined behavior; 7 found small but significant differences favoring nonexposed adolescents, with small effect sizes. Eight examined cognition/school performance; 6 reported significantly lower scores on language and memory tasks among adolescents with prenatal cocaine exposure, with varying effect sizes. Eight examined brain structure/function and reported morphologic differences with few functional differences; 3 examined physiologic responses with discordant findings. Most studies controlled for other prenatal exposures, caregiving environment, and violence exposure.

Conclusions Consistent with findings among younger children, prenatal cocaine exposure (mildly) increases the risk for less favorable adolescent functioning. Although the clinical importance of differences often is unknown, the caregiving environment and violence exposure pose additional threats.
Commentary

Studies continue to disprove the once popular belief that prenatal cocaine exposure predestines a generation of cocaine-exposed children to behavioral, physical, and neurological disabilities. As with prior studies examining the effects of prenatal cocaine exposure on neurodevelopmental outcomes, Buckingham-Howes et al have found that although prenatal cocaine exposure may be associated with behavioral effects, conclusions remain difficult to ascertain due to limited standardization of methodology and instruments to measure outcomes, small effect size differences between prenatal cocaine exposed and nonexposed comparison groups, insufficient reporting of the clinical and functional implications of these differences, and the coexistence of a variety of environmental factors, all of which may confound results. This latter point deserves additional emphasis, as the authors found that regardless of prenatal cocaine exposures, adolescents from similarly disadvantaged backgrounds scored lower than average on a range of neurodevelopmental measures. The roles of poverty, secure parent-child relationships, and violence exposure are critical in predicting developmental outcomes. This review further emphasizes that additional environmental factors, including other prenatal toxin exposure and socioeconomic stress, impact the effects of prenatal cocaine exposure. The mechanistic links between environmental stressors and neurodevelopmental sequelae is an essential area for future research, informing public health initiatives on optimizing behavioral, social, and academic outcomes for these vulnerable children.

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References