REL Appalachia Ask A REL Response

Early Childhood
June 2018

Question:

What research is available about the effects of opioid or heroin prenatal exposure on learning and development?

Response:

Thank you for your request to our REL Reference Desk regarding evidence-based information about the effects of prenatal opioid exposure on learning and development. Ask A REL is a collaborative reference desk service provided by the 10 Regional Educational Laboratories (RELs) that, by design, functions much in the same way as a technical reference library. Ask A REL provides references, referrals, and brief responses in the form of citations in response to questions about available education research.

Following an established REL Appalachia research protocol, we searched for peer-reviewed articles and other research reports on the effects of prenatal opioid exposure on learning and development. We focused on identifying resources that specifically addressed the effects of prenatal opioid or heroin exposure on learning and included resources about its effect on development, which dominate the body of literature. The sources included ERIC and other federally funded databases and organizations, research institutions, academic research databases, and general Internet search engines. For more details, please see the methods section at the end of this document.

The research team did not evaluate the quality of the resources provided in this response; we offer them only for your reference. Also, the search included the most commonly used research databases and search engines to produce the references presented here, but the references are not necessarily comprehensive, and other relevant references and resources may exist. References are listed in alphabetical order, not necessarily in order of relevance.

References

Baldacchino, A., Arbuckle, K., Petrie, D. J., & McCowan, C. (2014). Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: a systematic review and meta-analysis. *BMC Psychiatry*, *14*(1), 104. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/24708875

From the abstract: "*Background*: It is assumed within the accumulated literature that children born of pregnant opioid dependent mothers have impaired neurobehavioral function as a consequence of chronic intrauterine opioid use. *Methods*: Quantitative and systematic review of the literature on the consequences of chronic maternal opioid use during pregnancy on neurobehavioral function of children was conducted using the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. We searched Cinahl, EMBASE, PsychINFO and MEDLINE between the periods of January 1995 to January 2012. *Results*: There were only 5 studies out of the 200 identified that quantitatively reported on neurobehavioral function of children after maternal opioid use during pregnancy. All 5 were case control studies with the number of exposed subjects within the studies ranging from 33–143 and 45–85 for the controls. This meta-analysis showed no significant impairments, at a non-conservative significance level of $p < 0.05$, for cognitive, psychomotor or observed behavioural outcomes for chronic intra-uterine exposed infants and pre-school children compared to non-exposed infants and children. However, all domains suggested a trend to poor outcomes in infants/children of opioid using mothers. The magnitude of all possible effects was small according to Cohen's benchmark criteria. *Conclusions*: Chronic intra-uterine opioid exposed infants and pre-school children experienced no significant impairment in neurobehavioral outcomes when compared to non-exposed peers, although in all domains there was a trend to poorer outcomes. The findings of this review are limited by the small number of studies analysed, the heterogenous populations and small numbers within the individual studies. Longitudinal studies are needed to determine if any neuropsychological impairments appear after the age of 5 years and to help investigate further the role of environmental risk factors on the effect of 'core' phenotypes."

Bandstra, E. S., Morrow, C. E., Mansoor, E., & Accornero, V. H. (2010). Prenatal drug exposure: Infant and toddler outcomes. *Journal of Addictive Diseases*, *29*(2), 245–258. Retrieved from http://www.uky.edu/~sbarron/psy459/discussions/article1.pdf

From the abstract: "This manuscript provides an overview of the current scientific literature on the impact of maternal drug use, specifically opioids and cocaine, during pregnancy on the acute and long-term outcomes of infants and toddlers from birth through age 3 years. Emphasis with regard to opioids is placed on heroin and opioid substitutes used to treat opioid addiction, including methadone, which has long been regarded as the standard of care in pregnancy, and buprenorphine, which is increasingly being investigated and prescribed as an alternative to methadone. Controlled studies comparing methadone at high and low doses, as well as those comparing methadone with buprenorphine, are highlighted and the diagnosis and management of neonatal abstinence syndrome is discussed. Over the past two decades, attention of the scientific and lay communities has also been focused on the potential adverse effects of cocaine and crack cocaine, especially during the height of the cocaine epidemic in the United States. Herein, the findings are summarized from prospective studies comparing cocaine-exposed with non-cocaine-exposed infants and toddlers with respect to anthropometric growth, infant neurobehavior, visual and auditory function, and cognitive, motor, and language development. The potentially stigmatizing label of the so-called "crack baby" preceded the evidence now

accumulating from well-designed prospective investigations that have revealed less severe sequelae in the majority of prenatally exposed infants than originally anticipated. In contrast to opioids, which may produce neonatal abstinence syndrome and infant neurobehavioral deficits, prenatal cocaine exposure appears to be associated with what has been described as statistically significant but subtle decrements in neurobehavioral, cognitive, and language function, especially when viewed in the context of other exposures and the caregiving environment which may mediate or moderate the effects. Whether these early findings may herald more significant learning and behavioral problems during school-age and adolescence when the child is inevitably confronted with increasing social and academic challenges is the subject of ongoing longitudinal research."

Konijnenberg, C. & Melinder, A. (2014). Visual selective attention is impaired in children prenatally exposed to opioid agonist medication. *European Addiction Research*, *21*(2), 63–70. Retrieved from https://www.researchgate.net/profile/Annika_Melinder/publication/268450675_Visual_Selective_Attention_Is_Impaired_in_Children_Prenatally_Exposed_to_Opioid_Agonist_Medication/links/56a9d52708aef6e05df2e057.pdf

From the abstract: "*Aims*: To examine whether prenatal exposure to opioid agonist medication is associated with visual selective attention and general attention problems in early childhood. *Method*: Twenty-two children (mean age = 52.17 months, SD = 1.81) prenatally exposed to methadone, 9 children (mean age = 52.41 months, SD = 1.42) prenatally exposed to buprenorphine and 25 nonexposed comparison children (mean age = 51.44 months, SD = 1.31) were tested. Visual selective attention was measured with a Tobii 1750 Eye Tracker using a spatial negative priming paradigm. Attention problems were measured using the Child Behavior Checklist. *Results*: The comparison group demonstrated a larger spatial negative priming effect (mean = 23.50, SD = 45.50) than the exposed group [mean = -6.84, SD = 86.39, $F(1,50) = 5.91$, $p = 0.019$, $\eta^2 = 0.11$]. No difference in reported attention problems was found [$F(1,51) = 1.63$, $p = 0.21$, $\eta^2 = 0.03$]. Neonatal abstinence syndrome and prenatal exposure to marijuana were found to predict slower saccade latencies in the exposed group (b = 54.55, SE = 23.56, p = 0.03 and b = 88.86, SE = 32.07, p = 0.01, respectively). *Conclusion*: Although exposed children did not appear to have attention deficits in daily life, lower performance on the SNP task indicates subtle alteration in the attention system."

Levine, T. A. & Woodward, L. J. (2018). Early inhibitory control and working memory abilities of children prenatally exposed to methadone. *Early Human Development*, *116*, 68–75. Retrieved from https://www.sciencedirect.com/science/article/pii/S0378378217305054

From the abstract: "Background: Methadone maintenance is the most common method of treating opioid-dependent pregnant women. However, little is known about the impact of prenatal methadone exposure on child neurocognitive development. Aims: To examine the early executive functioning of children born to methadone-maintained mothers, and to assess relations between executive functioning and later emotional and behavioral adjustment. Study design: Prospective longitudinal study. Participants: The sample

consisted of 68 methadone-exposed children and 88 non-methadone-exposed children. Outcome measures: At age 2 years, children's inhibitory control and working memory were assessed using the Snack Delay and Three Boxes tasks. At 2 and 4.5 years, their emotional and behavioral adjustment was assessed using the caregiver-completed Strengths and Difficulties Questionnaire. Results: Methadone-exposed children had poorer inhibitory control than non-exposed children ($p < 0.0001$). These differences were explained by maternal education and prenatal benzodiazepine use. With respect to working memory, although both groups performed similarly on the first trial set, non-exposed children significantly improved their performance on the second trial set ($p = 0.002$), while methadone-exposed children did not ($p = 0.92$). Inhibitory control at age 2 years was predictive of higher conduct ($p = 0.001$), hyperactivity ($p = 0.0001$), peer relationship ($p = 0.02$), and total ($p < 0.0001$) problems at 4.5 years even after adjustment for behavioral problems at 2 years. Conclusions: Methadone-exposed children demonstrate difficulties with inhibitory control and possibly sustained attention/learning. These difficulties were explained by factors correlated with maternal prenatal methadone use. Longer-term follow-up of these children is needed to understand the effects of prenatal methadone exposure and related maternal factors on executive functioning and behavioral adjustment."

Nair, P., Black, M. M., Ackerman, J. P., Schuler, M. E., & Keane, V. A. (2008). Children's cognitive-behavioral functioning at age 6 and 7: Prenatal drug exposure and caregiving environment. *Ambulatory Pediatrics*, *8*(3), 154–162. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2766549/

From the abstract: "Objective: The aim of this study was to examine how prenatal drug exposure (PDE) and caregiving environment relate to cognitive, academic, and behavioral performance at ages 6 and 7. Methods: A longitudinal follow-up was conducted of 111 children with PDE and a community cohort of 62 non–drug-exposed children (N = 173). Children completed standardized tests of cognition (Stanford-Binet Intelligence Scales, Fourth Edition [SB-IV]) and academic performance (Wide Range Achievement Test 3). Caregivers completed ratings of child behavior problems (Child Behavior Checklist [CBCL]). Multivariate analyses were conducted, adjusting for gender, prenatal tobacco exposure, number of caregiver placement changes, and 3 caregiver variables assessed at age 7, including depressive symptoms, employment status, and public assistance status. Results: After adjusting for perinatal and environmental variables, there were no significant exposure-group differences in cognition, academic performance, or behavior problems. In comparison with males, females had higher scores on overall IQ and 4 of 8 SB-IV subtests, fewer caregiver-reported attention and aggression problems, and higher reading achievement scores. There were no significant gender-by-group interactions. Conclusion: When analyses were adjusted for perinatal and environmental variables, most associations between PDE and cognitive-behavioral functioning were attenuated. Regardless of drug exposure history, males performed more poorly than females on multiple cognitive-behavioral indices. Both exposed and nonexposed children were from low-income families and obtained scores substantially below normative expectations."

Note. "Children were assigned to the PDE group if their mother admitted using cocaine and/or heroin at least twice/week for the final six months of pregnancy or if they or their mother had a positive toxicology screen for heroin or cocaine" (p. 3).

Nygaard, E., Moe, V., Slinning, K., & Walhovd, K. B. (2015). Longitudinal cognitive development of children born to mothers with opioid and polysubstance use. *Pediatric Research*, *78*(3), 330–335. Retrieved from https://www.nature.com/articles/pr201595.pdf

From the abstract: "Background: Previous studies indicate an increased risk for neuropsychological difficulties in young children prenatally exposed to opioids and polysubstances, but longitudinal information is scarce. The present longitudinal study investigated whether these waned, persisted, or increased over time. Methods: The cognitive functioning of 72 children with prenatal opioid and polysubstance exposure and 58 children without any established prenatal risk was assessed at 1, 2, 3, 4½, and 8½ y. Results: The exposed boys had significantly and stably lower levels of cognitive functioning than the control group, whereas there were increasing differences over time for the girls. The exposed group had significantly lower IQ scores than the control group on Wechsler Intelligence Scale for Children—Revised at 8½ y after controlling for earlier cognitive abilities, and for children who were permanently placed in adoptive/foster homes before 1 y of age and whose mothers used heroin as their main drug during pregnancy (B = 17.04, 95% CI 8.69–25.38, P < 0.001). Conclusion: While effects of prenatal substance exposure cannot be isolated, group effects on cognition rather increased than waned over time, even in adoptive/foster children with minimal postnatal risk."

Nygaard, E., Slinning, K., Moe, V., & Walhovd, K. B. (2017). Cognitive function of youths born to mothers with opioid and poly-substance abuse problems during pregnancy. *Child Neuropsychology*, *23*(2), 159–187. Retrieved from https://www.tandfonline.com/doi/pdf/10.1080/09297049.2015.1092509?needAccess=true

From the abstract: "Previous research has provided inconclusive evidence regarding the neuropsychological difficulties of children born to mothers partaking in opioid or poly-drug use during pregnancy. Little is known about how these children fare as they get older. The present longitudinal study includes follow-up data on 45 children born to mothers who used heroin and poly-drugs and a group of 48 children without prenatal drug exposure. Most of the drug-exposed youths were placed in permanent foster or adoptive homes before one year of age. The youths (ages 17 to 21) were administered 10 neuropsychological tests. The drug-exposed youths had cognitive and fine motor functions within the normal range compared to population norms but performed significantly worse than the non-exposed group. There were indications of generally lower cognitive functions rather than specific problems with executive functioning. Lower mean birthweight in the risk group (619 grams mean difference, p < .001) only partially mediated the group differences in cognitive functioning. There was a tendency for youths who had few and early changes in their caregivers or who were born to mothers who had used the least number of different drugs during pregnancy to have the best cognitive scores. The study indicates that youths born to

mothers who used multiple drugs during pregnancy are vulnerable relative to their peers within a wide range of cognitive functions. The vulnerability seems to be related not only to the mother's drug use during pregnancy but also to factors such as birthweight and unstable parental care during infancy."

Oei, J. L., Melhuish, E., Uebel, H., Azzam, N., Breen, C., Burns, L., … Wright, I. M. (2017). Neonatal abstinence syndrome and high school performance. *Pediatrics*, *139*(2), 1–10. Retrieved from http://pediatrics.aappublications.org/content/139/2/e20162651.long

From the abstract: "Background and objectives: Little is known of the long-term, including school, outcomes of children diagnosed with Neonatal abstinence syndrome (NAS) (*International Statistical Classification of Disease and Related Problems* [10th Edition], Australian Modification, P96.1). Methods: Linked analysis of health and curriculum-based test data for all children born in the state of New South Wales (NSW), Australia, between 2000 and 2006. Children with NAS (*n* = 2234) were compared with a control group matched for gestation, socioeconomic status, and gender (*n* = 4330, control) and with other NSW children (*n* = 598 265, population) for results on the National Assessment Program: Literacy and Numeracy, in grades 3, 5, and 7. Results: Mean test scores (range 0–1000) for children with NAS were significantly lower in grade 3 (359 vs control: 410 vs population: 421). The deficit was progressive. By grade 7, children with NAS scored lower than other children in grade 5. The risk of not meeting minimum standards was independently associated with NAS (adjusted odds ratio [aOR], 2.5; 95% confidence interval [CI], 2.2–2.7), indigenous status (aOR, 2.2; 95% CI, 2.2–2.3), male gender (aOR, 1.3; 95% CI, 1.3–1.4), and low parental education (aOR, 1.5; 95% CI, 1.1–1.6), with all *P*s < .001. Conclusions: A neonatal diagnostic code of NAS is strongly associated with poor and deteriorating school performance. Parental education may decrease the risk of failure. Children with NAS and their families must be identified early and provided with support to minimize the consequences of poor educational outcomes."

Sandtorv, L. B., Fevang, S. K. E., Nilsen, S. A., Boe, T., Gjestad, R., Haugland, S., & Elgen, I. B. (2018). Symptoms associated with attention deficit/hyperactivity disorder and autism spectrum disorders in school-aged children prenatally exposed to substances. *Substance Abuse: Research and Treatment*, *12*, 1–8. Retrieved from http://journals.sagepub.com/doi/pdf/10.1177/1178221818765773

From the abstract: "Prenatal exposure to substances may influence a child's neurodevelopment and impact on subsequent mental health. In a hospital-based population of school-aged children prenatally exposed to opiates and a number of illicit substances (n = 57), we evaluated mental health symptoms associated with attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) using the Swanson, Nolan, and Pelham Questionnaire, revision IV (SNAP-IV) and the Autism Spectrum Screening Questionnaire (ASSQ) and compared the scores to a reference group which comprised children from the population-based Bergen Child Study (n = 171). Prenatally exposed children had significantly higher SNAP-IV scores associated with ADHD symptoms in both areas of inattention and hyperactivity/impulsivity and also reported a higher ASSQ

score related to an increased number of symptoms associated with ASD, compared with the reference group. Of tested predictors of mental health outcomes in the exposed group, the intelligence quotient was a strong predictor of most mental health outcomes, and neonatal abstinence syndrome was a predictor of inattention. In conclusion, prenatally exposed children had more mental health symptoms associated with ADHD and ASD, compared with the reference group."

Additional Organizations to Consult

AIR: Center for Multi-System Solutions to the Opioid Epidemic: https://www.air.org/center/center-multi-system-solutions-opioid-epidemic

From the website: "Opioid misuse, overdose, and death has become a national public health emergency. More than 100 people a day die from an opioid overdose and the number of people being treated for opioid overuse continues to rise (Centers for Disease Control and Prevention). Developing solutions to this complex epidemic will require government agencies, private industry, and communities to work together across systems, including health care, public health, law enforcement, mental health, social services, and insurance providers. The American Institutes for Research (AIR) has an experienced team with broad expertise in preventing substance misuse and expanding access to evidence-based treatment and recovery for addiction and substance use disorders, addressing mental and behavioral health issues, and facilitating trauma-informed care."

National Center on Substance Abuse and Child Welfare: https://ncsacw.samhsa.gov/

From the website: "NCSACW is a national resource center providing information, expert consultation, training and technical assistance to child welfare, dependency court and substance abuse treatment professionals to improve safety, permanency, well-being and recovery outcomes for children, parents and families."

Webpage on opioid use disorders and medication-assisted treatment in pregnancy: https://ncsacw.samhsa.gov/resources/opioid-use-disorders-and-medication-assisted-treatment/default.aspx

Methods

Keywords and Search Strings

The following keywords and search strings were used to search the reference databases and other sources:

- (Prenatal OR in utero) AND (opioid OR heroin) AND (learning OR school performance OR academic outcomes OR longitudinal effects OR cognitive OR behavior*)

Databases and Resources

We searched ERIC, a free online library of more than 1.6 million citations of education research sponsored by the Institute of Education Sciences (IES), for relevant resources. Additionally, we searched the academic database ProQuest, Google Scholar, and the commercial search engine Google.

Reference Search and Selection Criteria

In reviewing resources, Reference Desk researchers consider—among other things—these four factors:

- Date of the publication: Searches cover the most current information (i.e., within the last ten years), except in the case of nationally known seminal resources.
- Search priorities of reference sources: Search priorities include IES, nationally funded, and certain other vetted sources known for strict attention to research protocols. Applicable resources must be publicly available online and in English.
- Methodology: The following methodological priorities/considerations guide the review and selection of the references: (a) study types—randomized controlled trials, quasi experiments, surveys, descriptive data analyses, literature reviews, policy briefs, etc., generally in this order; (b) target population, samples (representativeness of the target population, sample size, volunteered or randomly selected), study duration, etc.; (c) limitations, generalizability of the findings and conclusions, etc.
- Existing knowledge base: Vetted resources (e.g., peer-reviewed research journals) are the primary focus, but the research base is occasionally slim or nonexistent. In those cases, the best resources available may include, for example, reports, white papers, guides, reviews in non-peer-reviewed journals, newspaper articles, interviews with content specialists, and organization websites.

Resources included in this document were last accessed on May 31, 2018. URLs, descriptions, and content included here were current at that time.

This memorandum is one in a series of quick-turnaround responses to specific questions posed by education stakeholders in the Appalachia region (Kentucky, Tennessee, Virginia, and West Virginia), which is served by the Regional Educational Laboratory Appalachia (REL AP) at SRI International. This Ask A REL response was developed by REL AP under Contract ED-IES-17-C-0004 from the U.S. Department of Education, Institute of Education Sciences, administered by SRI International. The content does not necessarily reflect the views or policies of IES or the U.S. Department of Education, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. government.