

A Review of Neurobehavioral Challenges in Children Exposed Prenatally to Intrauterine Opioid

Kamaleddin Alaedini,¹ Kaveh Haddadi,^{2,*} and Leila Asadian³

¹Addiction Studies PhD Candidate, School of Advanced Medical Technologies, Tehran University of Medical Sciences, Tehran, IR Iran

²Department of Neurosurgery, Emam Khomeini Hospital, Orthopedic Research Center, Mazandaran University of Medical Sciences, Sari, IR Iran

³Orthopedic Research Center, Mazandaran University of Medical Sciences, Sari, IR Iran

*Correspondence: Kaveh Haddadi, Associated Professor, Neurosurgeon, Department of Neurosurgery, Emam Khomeini Hospital, Orthopedic Research Center, Mazandaran University of Medical Sciences, Sari, IR Iran. Tel: +98-9113918316, E-mail: kh568hd@yahoo.com

Received 2016 October 02; Revised 2017 February 01; Accepted 2017 February 08.

Abstract

Context: Substance abuse has remained a worldwide issue for many years and in recent decades there has been a major growth in the number of individuals consuming opioids. Several studies have discovered that young kids who have been exposed to opioids develop greater damages in overall intellectual capabilities and neurobehavioral functions than non-exposed children.

Evidence Acquisition: The purpose of this study was to evaluate the surviving texts on the incidence of challenging behavior among kids due to prenatal medication contact. Overall, out of 84 identified manuscripts, 18 were established to consider intellectual, psychomotor, and behavior consequences in opioid-exposed infants, precollege and college children when matched with healthy no-opioid-exposed controls.

Results: The results indicate that children exposed to opioid in utero may be cognitively affected over time, even once located in stable families on an actual early age. Somewhat, susceptibilities seem to rise by age for girls, and the unprotected boys persist behind non-exposed boys entirely through infancy and into college age. Therefore, there looks to be a constant deleterious consequence of factors associated with prenatal medication contact over time.

Conclusions: The results indicate children exposed to opioid in utero may be cognitively affected over time, even once located in stable families on an actual early age. The natural susceptibilities of prenatally drug-exposed children can affect initial intellectual skills which yet again are extremely associated with advanced mental capabilities. It is feasible that pre- and postnatal genetic susceptibilities and ecological issues cooperate in a transactional method through the child's lifespan.

Keywords: Neurobehavioral, Prenatal Exposure, Review, Opioid

1. Context

Substance abuse has remained a worldwide issue for many years and there has been a major growth in the number of individuals consuming opioids in recent decades (1). The first valid record of opium dependence was in about 200 years ago (2). Morphine was removed in 1804, while heroin was produced first in 1874, and dependence on opioids developed extra public due to their profitable creation (3). A growth in the occurrence of morphine and heroin habit among females was prominent as early as about 100 years ago (4); but, newborns were not believed to be exposed as it was supposed that morphine use amongst females was related to infertility and damage of erotic desire. That misconception modified since the initial described event in a neonate about 1987 (5, 6) who displayed signs of opioid withdrawal at delivery, identified by means of inherited morphinism. After that, augmented reports of congenital morphinism caused an important consideration in the view of obstetricians and pediatricians (6, 7). Inherited morphinism was situated afterward retitled in place of ab-

stinence syndrome in neonates. Methadone was presented as an additional management of opioid dependence in 1964 (8). Methadone consumption during perinatal period was at primary supposed to stay unrelated to withdrawal in neonates; nevertheless, later knowledge denied this original misimpression (9). Buprenorphine was accepted as a substitute to methadone for opium dependence in Europe and the USA (10). Consumption of buprenorphine in perinatal period similarly leads to Neonatal abstinence syndrome (NAS) that is a result of the sudden discontinuation (10).

During pregnancy, medications can pass through the placenta and remain side effects on the fetus. This result is frequently inflexible to calculate as there are additional features that might be measured by means of taking a superior consequence on children's outcomes, for instance, the value of carefulness or the environs (11).

While the majority of children born to mothers who consume opioids suffer from neonatal abstinence syndrome (12), the limited trainings of children provide the possibility of complications inside arenas associated with

management, control, and responsiveness. Here is some evidence interested in neonatal abstinence syndrome and natal constraints none the less rarer reports on neurodevelopmental questions nearby prenatal contact to opioids (10, 11).

Several investigations have shown that children who have been exposed to opioids develop greater damages in overall intellectual capabilities and neurobehavioral functions than non-exposed children (Table 1).

Since we have been faced significantly with increased cognitive and behavioral disorders in children referring to our clinics due to various physical illness like trauma, spine diseases, and hydrocephalous (13-15), we decided to design the current study after taking a careful history from the patients family.

The aim of this study was to review the surviving literature on the incidence of puzzling performance among kids with prenatal medication contact.

2. Evidence Acquisition

We investigated PubMed and Ovid and Google scholar databases using key words including cognitive, behavior, prenatal exposure, and opium. This was shadowed by the word neurobehavioral which remained then substituted using a series of expressions recounting terms of a list of cognitive and psychomotor examinations. Exclusion criteria were texts published in any language other than English. In overall, 84 articles were obtained from which, 18 were established to consider the behavioral, psychomotor, and cognitive consequences in opioid unprotected infants and children when matched with healthy no-opioid unprotected controls.

3. Results

3.1. Epidemiology

Even though heroin abuse has stayed comparatively persistent in developed countries, it creates greater concern than before in developing countries (16-18). The abuse of pain relieving drugs has increased among pregnant women (19). A current study described that 6% of mothers used opium for more than 30 days during gravidity (20, 21).

In England, it is estimated that about 280,000 persons use opioids among whom 30% are females (22-24). In Scotland, 925 pregnant women described medication misapplication in 2009 - 2010, giving a ratio of 16.1 per 1,000 gravidities, by way of opioids informed in 506 (55%) of these conditions (25).

Above hemi the pregnant mothers who account drug use are opioid reliant on through significant rise in danger to equally mother and probable child (25, 26). Unfortunately we do not have any definitive document and record about substance abuse in pregnant women in Iran.

3.2. General Features

Heroin exploitation is more common among mothers who are single, jobless, less cultured, and less protected. Gravidities amongst heroin-abusing women are frequently unintended and are accompanied by poor prenatal care. These mothers commonly have low living standards, and regularly have numerous public, physical, nutritional and psychological health difficulties (16). Babies born to these women generally are premature, commonly have low birth weights, and are frequently growth restricted.

Many kids born to heroin-abusing mothers progress NAS closely afterward birth (17).

Methadone, as an artificial whole m-opioid receptor agonist, has been developed in the ordinary care of gravid females by opioid dependence. Methadone management throughout pregnancy has improved obstetric attention, reduced illegal drug consumption, and promoted fetal outcomes. However, methadone usage has remained correlated with the amplified occurrence of NAS (18). Buprenorphine is a semisynthetic partial m-opioid receptor agonist and a potent k-opioid receptor antagonist that has been established to be correspondingly harmless; thus, it has become a real supernumerary to methadone for opioid dependence through pregnancy (27). Several studies confirm that buprenorphine maintenance usage in gravidity is similar or superior to methadone management by respect to NAS (19, 20). A new meta-analysis did not approve the priority of one over the other (21).

It is well recognized that prenatal alcohol exposure can have unfavorable effects on the child's mental skills (26). Single of the greater trainings of prenatal cocaine contact is a Parental Lifestyle Training, which comprises more than 1100 children in contact with cocaine (27), of whom several hundreds have been surveyed up to fifteen years of age (28). These trainings have indicated that prenatal cocaine experience is associated with difficulties in continued responsiveness and behavioral habits even after adjustment for covariates (29).

The majority of kids born to mothers who consume opioids suffer from NAS (12). The limited studies on kids direct the probability of difficulties in the fields linked to decision-making, control, and responsiveness (30-32) and behavior regulation (33).

Fine motor skills, which are regularly correlated with executive control (34), have similarly been established to

Table 1. Neurobehavioral Functions that Affected Children Who Have Been Exposed to Opioids

Key Territory	Description
Memory	Child's ability to hold and employ information over brief times of time, in the sequence of enduring cognitive activities
Psychomotor	The child's ability to join thoughts with muscle activities
Executive functions	Child's ability to analyze conditions, strategy and take action, focus and preserve attention, and regulate actions as needed to acquire the job done
Nonverbal processing	Child's ability to establish the visual-spatial field, adapt to new or original situations, and/or precisely read nonverbal signals and signs.
Overall cognitive	Child's ability to study and solve problems
Social/emotional adjustment	Child's skill to cooperate with others, containing helping themselves and self-discipline.
Language	Child's ability to recognize and use language together

be poorer amongst young children born to mothers abusing opioid and poly-drug during gravidity (35). Particular studies have found that motor aptitudes are the most damaged functional area (36), while other studies have not established noteworthy group dissimilarities in motor capabilities (37).

The uncommon documents on the mature off spring of opioid-dependent mothers show a great possibility of illegal activities, substance abuse, and joblessness (38); these have also been reported for persons with fetal alcohol range disorder (39). Complications by policy making utilities, such as self-regulation and attention, in young children might come to be more severe as they turn into adults. Executive utilities usually endure to advance through the teenage years into young middle age (40). It is imaginable that children's prior susceptibility in these areas comes to be more thoughtful lengthways the developing route as their environment spaces aggregate strains on these multifaceted executive utilities. This can be particularly factual on the age once young adults generally take away from their parents and additional care systems that have surveyed them through their background. Therefore, it is a concern that almost no studies certificate the growth of children into young adulthood who were unprotected prenatally to opioids and various medications.

3.3. Pathophysiology and Etiology

Investigation on animal has brought that prenatal opium contact changes the myelin sheath in the developed brain (41). Numerous animal studies have shown that prenatal opioid exposure disturbs some vital neurotransmitter systems (42). Consequently, it is possible that prenatal opioid contact has an adverse neurological outcome on humanoid fetuses. Children born to mothers involved in opioid and poly-substance consumption during pregnancy regularly have less birth weight than control groups (43,

44). Low birth weight has been proven to be a prognosticator of later cognitive capacities (45, 46), socio-emotional functioning, decision-making functioning, academic success and neuroanatomical physiognomies, even for normal birth weight variants (32). Birth weight is in association not only with hereditarily strong minded body mass, but also with prenatal environs deviations such as mother anxiety in gravidity (43), maternal food ingestion during pregnancy and maternal substance abuse in pregnancy, such as smoking and alcohol use (39). But, it is also possible that maternal consumption of opioids or substances affects birth weight (43). Therefore, birth weight might be a facilitating cause for some undesirable consequences of prenatal medication experience.

It has been assumed that improvement of the post-partum atmosphere can pay compensation for the natural susceptibility of these children. For instance, development in a steady and home-based family was established to be the maximum essential defensive issue in escaping from secondary difficulties in a great study of population with fetal alcohol syndrome (47). Accordingly, children by initial assignment in respectable adoptive or adoptive families can experience positive growth in excess of time.

The studies have shown that children prenatally exposed to opioids take practically completely motivated on infancy and babyhood. They have established that infants born to mothers consuming opioid during gravidity demonstrate less intellectual presentation and disturbed regulation than no exposed infants (48). Opioid children have similarly indicated less neuroanatomical capacities and directories of less significant development of neural tracts than controls (47-49).

Animal studies have shown prenatal opioid contact has teratogenic special effects, disturbance in neuronal migration, and cell death (50, 51), reduction of dendrite length and division amount in pyramidal neurons in the somatosensory cortex and distractions to numerous neu-

rotransmitter organizations (42).

There might likewise be dependence on gender properties of prenatal contact to opioids, as they have been originated from pregnancy exposure to cocaine (52, 53). While some have established prenatally opioid-exposed boys to be more susceptible than girls, others have not indicated any severances. Therefore, the question about gender specific susceptibility for opioid exposure is unsettled (52, 54).

Based on some studies, due to the absence of information of thinkable confusing differences, it is incredible to distinguish why the opioid exposed boys, not girls, required inferior intellectual aptitudes up to 3 years of age. Boys could be extra susceptible than girls to likely prenatal neurotoxins medication contact (52). Preceding results propose that new born boys frequently want more co-regulation than girls. At hand is a noticeable mannish dominance for nearly entirely euro-developmental complaints that rise before college age, as well as attention insufficiency complaint with hyperactivity (53). Several authors state that 6 year old cocaine exposed boys, not girls, display more hyperactivity and mental complications than no exposed peers (54). Standard gender differences and a fewer ideal mannish prenatal initial point might inter relate by neonatal abstinences and augmented regulation difficulties regularly establish between drug unprotected kids (48).

The natural susceptibilities of prenatally drug exposed children can affect initial intellectual skills which are extremely associated with advanced cognitive capabilities. However, the prenatal susceptibilities can likewise have a constant direct influence on the capability to obtain novel abilities. Special effects of maternal opioid usage on multifaceted cognition and self-regulation, such as decision-making functions, are able to be detected when these behaviors progress during school age years and further.

It is feasible that pre and postpartum hereditary susceptibilities and ecological issues cooperate in a transactional method in the child's lifespan (55). Therefore, natural composition, including genomic makeup, diet, and medication contact, might interact by future ecological elements, such as parent caregiving, excellence of daytime care and college, in manipulating the cognitive growth of the kid. Consequently, an imaginable clarification is that these drug-exposed children can bring in early on from a steady situation with especially designated foster and adoptive parents. When come to precollege and college, they look for a more multifaceted and fewer protecting public environment with progressively greater burdens that challenge their susceptibility. For instance, some studies point to particular care difficulties of opioid-exposed kids that might affect their performance and emotion regulation. It is similarly probable that drug unprotected chil-

dren are more susceptible to future ecological risk factors (56). Girls' overall superiority for emotional harms rising in teenage years can also initiate to interrelate by the susceptibility of the exposed girls at an even previously age.

There were signs of an association among the amount of different medications and intellectual skills. The extent of medications to which the children were prenatally exposed can take aggregate or synergistic toxicological properties, and then it might likewise be a suggestion of the harshness of the mothers overall state and working.

3.4. Management and Prevention

Developmental consequences of prenatally drug-exposed children are determined by factors including the particular drug or drugs, amount, and timing of prenatal exposure as well as pre- and postnatal ecological situations, comprising sustained caregiver drug use, mental symptoms, eminence of the home-based environment, postnatal exposures to lead and other poisons, caregiver constancy, and kind of caregiver (57). Pregnancy is a sole period when a female may pursue treatment out of distress for the health and well-being of her child. To avoid postpartum substance abuse deterioration, interventions must effort on cessation rather than temporary abstinence. The continuing penalties of parental substance abuse on child development should be highlighted, and follow-up would continue into the postpartum period (58). Mediations that decrease substance abuse in the universal population are currently being examined in pregnant substance abusers with hopeful results.

Supplementary research is needed on the development of detailed interventions for drug-exposed infants and children. Every child must be individually evaluated for his or her collective risk factors, field of developmental difficulty, and the value of the caregiving environment. Developmental outcomes that may be enhanced by mediations arise early in life are personalized for particular problematic areas, and level of stress, emotional health functioning, continued substance abuse, and parenting interactions (57).

4. Conclusions

The results indicate children exposed to opioid in utero may be cognitively affected over time, even once located in stable families on an actual early age. Somewhat, susceptibilities seem to rise by age for girls, and the unprotected boys keep on overdue no exposed boys completely through early stages and into college age. Therefore, there looks to be a constant deleterious consequence of factors associated with prenatal medication contact over time.

The natural susceptibilities of prenatally drug exposed children can affect initial intellectual skills which yet again are extremely associated with advanced mental skills. It is feasible that pre and postpartum hereditary susceptibilities and ecological issues cooperate in a transactional method through the child's lifetime. Future studies are required to define if some neuropsychological damages seem afterward the age of 5 years and to aid explore additional character of ecological risk factors on the consequence of maternal opioid.

Footnotes

Conflict of Interest: None.

Funding/Support: None.

References

- Manchikanti L, Fellows B, Ailinani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. *Pain Physician*. 2010;**13**(5):401-35. [PubMed: 20859312].
- Heroin timeline . Heroin addiction 2013. Available from: www.heroinaddiction.com/herointimeline.html.
- Merry J. A social history of heroin addiction. *Br J Addict Alcohol Other Drugs*. 1975;**70**(3):307-10. [PubMed: 1103920].
- Courtwright D. Dark Paradise: Opiate Addiction in America before 1940. Cambridge: Harvard University Press; 1982.
- Menninger-Lerchenthal E. Die morphin krankheit der neugeborenen morphine stischer mutter Monatsschr. *F Kinderh*. 1934;**60**:182-93.
- Goodfriend MJ, Shey IA, Klein MD. The effects of maternal narcotic addiction on the newborn. *Am J Obstet Gynecol*. 1956;**71**(1):29-36. [PubMed: 13282969].
- Cobrinik RW, Hood RJ, Chusid E. The effect of maternal narcotic addiction on the newborn infant; review of literature and report of 22 cases. *Pediatrics*. 1959;**24**(2):288-304. [PubMed: 13674828].
- National Consensus Development Panel. Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. *JAMA*. 1998;**280**(22):1936-43. [PubMed: 9851480].
- Reddy AM, Harper RG, Stern G. Observations on heroin and methadone withdrawal in the newborn. *Pediatrics*. 1971;**48**(3):353-8. [PubMed: 5094335].
- Auriacombe M, Fatseas M, Dubernet J, Daulouede JP, Tignol J. French field experience with buprenorphine. *Am J Addict*. 2004;**13** Suppl 1:S17-28. doi: 10.1080/10550490490440780. [PubMed: 15204673].
- Center for Substance Abuse Treatment. Clinical guidelines for the use of buprenorphine in the treatment of opioid addiction. Treatment Improvement Protocol (TIP) series 40. Rockville: DHHS publication (SMA); 2004.
- Patrick SW, Schumacher RE, Benneyworth BD, Krans EE, McAllister JM, Davis MM. Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *JAMA*. 2012;**307**(18):1934-40. doi: 10.1001/jama.2012.3951. [PubMed: 22546608].
- Haddadi K. Outlines and outcomes of instrumented posterior fusion in the pediatric cervical spine: a review article. *J Pediatr Rev*. 2016;**4**(1).
- Haddadi K. Pediatric lumbar disc herniation: a review of manifestations, diagnosis and management. *J Pediatr Rev*. 2016;**4**(1).
- Haddadi K. Pediatric Endoscopic Third Ventriculostomy: A Narrative Review of Current Indications, Techniques and Complications. *J Pediatr Rev*. 2016;**4**(2).
- Carrieri MP, Amass L, Lucas GM, Vlahov D, Wodak A, Woody GE. Buprenorphine use: the international experience. *Clin Infect Dis*. 2006;**43** Suppl 4:S197-215. doi: 10.1086/508184. [PubMed: 17109307].
- Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CJ. Teratology and medications that affect the fetus. In: Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CJ, editors. *Williams Obstetrics*. New York: McGraw Hill; 2010. p. 328.
- Kaltenbach K, Berghella V, Finnegan L. Opioid dependence during pregnancy. Effects and management. *Obstet Gynecol Clin North Am*. 1998;**25**(1):139-51. [PubMed: 9547764].
- Rikshem M, Gossop M, Clausen T. From methadone to buprenorphine: changes during a 10 year period within a national opioid maintenance treatment programme. *J Subst Abuse Treat*. 2014;**46**(3):291-4. doi: 10.1016/j.jsat.2013.10.006. [PubMed: 24210532].
- Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, Arria AM, et al. Neonatal abstinence syndrome after methadone or buprenorphine exposure. *N Engl J Med*. 2010;**363**(24):2320-31. doi: 10.1056/NEJMoa1005359. [PubMed: 21142534].
- Minozzi S, Amato L, Bellisario C, Ferri M, Davoli M. Maintenance agonist treatments for opiate-dependent pregnant women. *Cochrane Database Syst Rev*. 2013(12):CD006318. doi: 10.1002/14651858.CD006318.pub3. [PubMed: 24366859].
- Buchi KF, Suarez C, Varner MW. The prevalence of prenatal opioid and other drug use in Utah. *Am J Perinatol*. 2013;**30**(3):241-4. doi: 10.1055/s-0032-1323586. [PubMed: 22879357].
- NICE . Drug Misuse: Psychosocial Interventions. London: National Institute for Health and Clinical Excellence; 2007.
- Keegan J, Parva M, Finnegan M, Gerson A, Belden M. Addiction in pregnancy. *J Addict Dis*. 2010;**29**(2):175-91. doi: 10.1080/10550881003684723. [PubMed: 20407975].
- Information Services Division . Drug misuse statistics in Scotland 2011. Available from: <http://www.isdscotland.org>.
- Flak AL, Su S, Bertrand J, Denny CH, Kesmodel US, Cogswell ME. The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. *Alcohol Clin Exp Res*. 2014;**38**(1):214-26. doi: 10.1111/acer.12214. [PubMed: 23905882].
- Bauer CR, Shankaran S, Bada HS, Lester B, Wright LL, Krause-Steinrauf H, et al. The Maternal Lifestyle Study: drug exposure during pregnancy and short-term maternal outcomes. *Am J Obstet Gynecol*. 2002;**186**(3):487-95. [PubMed: 11904612].
- Neonatal Research Network. The Maternal Lifestyle Study (MLS) 2014. Available from: https://neonatal.rti.org/about/mls_background.cfm.
- Ackerman JP, Riggins T, Black MM. A review of the effects of prenatal cocaine exposure among school-aged children. *Pediatrics*. 2010;**125**(3):554-65. doi: 10.1542/peds.2009-0637. [PubMed: 20142293].
- Melinder A, Konijnenberg C, Sarfi M. Deviant smooth pursuit in preschool children exposed prenatally to methadone or buprenorphine and tobacco affects integrative visuomotor capabilities. *Addiction*. 2013;**108**(12):2175-82. doi: 10.1111/add.12267. [PubMed: 23734878].
- Slinning K. Foster placed children prenatally exposed to poly-substances-attention-related problems at ages 2 and 4 1/2. *Eur Child Adolesc Psychiatry*. 2004;**13**(1):19-27. doi: 10.1007/s00787-004-0350-x. [PubMed: 14991428].
- Walhovd KB, Fjell AM, Espeseth T. Cognitive decline and brain pathology in aging-need for a dimensional, lifespan and systems vulnerability view. *Scand J Psychol*. 2014;**55**(3):244-54. doi: 10.1111/sjop.12120. [PubMed: 24730622].
- Hans SL. Prenatal drug exposure: behavioral functioning in late childhood and adolescence. *NIDA Res Monogr*. 1996;**164**:261-76. [PubMed: 8809876].
- Rigoli D, Piek JP, Kane R, Oosterlaan J. An examination of the relationship between motor coordination and executive functions in adolescents. *Dev Med Child Neurol*. 2012;**54**(11):1025-31. doi: 10.1111/j.1469-8749.2012.04403.x. [PubMed: 22845862].

35. Logan BA, Heller NA, Paul JA, Morrison DG, Brown M, Krishnan R, et al. Longitudinal Developmental Outcomes In The First Year In Opiate-exposed Infants: Role Of Prenatal Alcohol Exposure. *Alcohol Clin Exp Res*. 2011;**35**:40A.
36. Sundelin Wahlsten V, Sarman I. Neurobehavioural development of preschool-age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. *Acta Paediatr*. 2013;**102**(5):544-9. doi: [10.1111/apa.12210](https://doi.org/10.1111/apa.12210). [PubMed: 23432078].
37. van Baar A. Development of infants of drug dependent mothers. *J Child Psychol Psychiatry*. 1990;**31**(6):911-20. [PubMed: 2246341].
38. Skinner ML, Haggerty KP, Fleming CB, Catalano RF. Predicting functional resilience among young-adult children of opiate-dependent parents. *J Adolesc Health*. 2009;**44**(3):283-90. doi: [10.1016/j.jadohealth.2008.07.020](https://doi.org/10.1016/j.jadohealth.2008.07.020). [PubMed: 19237115].
39. Dorrie N, Focker M, Freunsch I, Hebebrand J. Fetal alcohol spectrum disorders. *Eur Child Adolesc Psychiatry*. 2014;**23**(10):863-75. doi: [10.1007/s00787-014-0571-6](https://doi.org/10.1007/s00787-014-0571-6). [PubMed: 24965796].
40. Tamnes CK, Ostby Y, Walhovd KB, Westlye LT, Due-Tønnessen P, Fjell AM. Neuroanatomical correlates of executive functions in children and adolescents: a magnetic resonance imaging (MRI) study of cortical thickness. *Neuropsychologia*. 2010;**48**(9):2496-508. doi: [10.1016/j.neuropsychologia.2010.04.024](https://doi.org/10.1016/j.neuropsychologia.2010.04.024). [PubMed: 20434470].
41. Sanchez ES, Bigbee JW, Fobbs W, Robinson SE, Sato-Bigbee C. Opioid addiction and pregnancy: perinatal exposure to buprenorphine affects myelination in the developing brain. *Glia*. 2008;**56**(9):1017-27. doi: [10.1002/glia.20675](https://doi.org/10.1002/glia.20675). [PubMed: 18381654].
42. Konijnenberg C, Melinder A. Prenatal exposure to methadone and buprenorphine: a review of the potential effects on cognitive development. *Child Neuropsychol*. 2011;**17**(5):495-519. doi: [10.1080/09297049.2011.553591](https://doi.org/10.1080/09297049.2011.553591). [PubMed: 21480011].
43. Creanga AA, Sabel JC, Ko JY, Wasserman CR, Shapiro-Mendoza CK, Taylor P, et al. Maternal drug use and its effect on neonates: a population-based study in Washington State. *Obstet Gynecol*. 2012;**119**(5):924-33. doi: [10.1097/AOG.0b013e31824ea276](https://doi.org/10.1097/AOG.0b013e31824ea276). [PubMed: 22525903].
44. Mactier H, Shipton D, Dryden C, Tappin DM. Reduced fetal growth in methadone-maintained pregnancies is not fully explained by smoking or socio-economic deprivation. *Addiction*. 2014;**109**(3):482-8. doi: [10.1111/add.12400](https://doi.org/10.1111/add.12400). [PubMed: 24321028].
45. Leitner Y, Fattal-Valevski A, Geva R, Bassan H, Posner E, Kutai M, et al. Six-year follow-up of children with intrauterine growth retardation: long-term, prospective study. *J Child Neurol*. 2000;**15**(12):781-6. doi: [10.1177/088307380001501202](https://doi.org/10.1177/088307380001501202). [PubMed: 11198491].
46. Monk C, Spicer J, Champagne FA. Linking prenatal maternal adversity to developmental outcomes in infants: the role of epigenetic pathways. *Dev Psychopathol*. 2012;**24**(4):1361-76. doi: [10.1017/S0954579412000764](https://doi.org/10.1017/S0954579412000764). [PubMed: 23062303].
47. Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. *J Dev Behav Pediatr*. 2004;**25**(4):228-38. [PubMed: 15308923].
48. Lester BM, Lagasse LL. Children of addicted women. *J Addict Dis*. 2010;**29**(2):259-76. doi: [10.1080/10550881003684921](https://doi.org/10.1080/10550881003684921). [PubMed: 20407981].
49. Walhovd KB, Watts R, Amlien I, Woodward LJ. Neural tract development of infants born to methadone-maintained mothers. *Pediatr Neurol*. 2012;**47**(1):1-6. doi: [10.1016/j.pediatrneurol.2012.04.008](https://doi.org/10.1016/j.pediatrneurol.2012.04.008). [PubMed: 22704008].
50. Walhovd KB, Westlye LT, Moe V, Slinning K, Due-Tønnessen P, Bjørnerud A, et al. White matter characteristics and cognition in prenatally opiate- and polysubstance-exposed children: a diffusion tensor imaging study. *AJNR Am J Neuroradiol*. 2010;**31**(5):894-900. doi: [10.3174/ajnr.A1957](https://doi.org/10.3174/ajnr.A1957). [PubMed: 20203117].
51. Wang Y, Han TZ. Prenatal exposure to heroin in mice elicits memory deficits that can be attributed to neuronal apoptosis. *Neuroscience*. 2009;**160**(2):330-8. doi: [10.1016/j.neuroscience.2009.02.058](https://doi.org/10.1016/j.neuroscience.2009.02.058). [PubMed: 19272431].
52. Lewis M, Kestler L. Gender differences in prenatal substance exposure. Washington DC: American Psychological Association; 2012.
53. Weinberg MK, Tronick EZ, Cohn JF, Olson KL. Gender differences in emotional expressivity and self-regulation during early infancy. *Dev Psychol*. 1999;**35**(1):175-88. [PubMed: 9923473].
54. Delaney-Black V, Covington C, Nordstrom B, Ager J, Janisse J, Hannigan JH, et al. Prenatal cocaine: quantity of exposure and gender moderation. *J Dev Behav Pediatr*. 2004;**25**(4):254-63. [PubMed: 15308926].
55. Sameroff A. A unified theory of development: a dialectic integration of nature and nurture. *Child Dev*. 2010;**81**(1):6-22. doi: [10.1111/j.1467-8624.2009.01378.x](https://doi.org/10.1111/j.1467-8624.2009.01378.x). [PubMed: 20331651].
56. Yumoto C, Jacobson SW, Jacobson JL. Fetal substance exposure and cumulative environmental risk in an African American cohort. *Child Dev*. 2008;**79**(6):1761-76. doi: [10.1111/j.1467-8624.2008.01224.x](https://doi.org/10.1111/j.1467-8624.2008.01224.x). [PubMed: 19037948].
57. Minnes S, Singer LT, Kirchner HL, Short E, Lewis B, Satayathum S, et al. The effects of prenatal cocaine exposure on problem behavior in children 4-10 years. *Neurotoxicol Teratol*. 2010;**32**(4):443-51. doi: [10.1016/j.ntt.2010.03.005](https://doi.org/10.1016/j.ntt.2010.03.005). [PubMed: 20227491].
58. Muhuri PK, Gfroerer JC. Substance use among women: associations with pregnancy, parenting, and race/ethnicity. *Matern Child Health J*. 2009;**13**(3):376-85. doi: [10.1007/s10995-008-0375-8](https://doi.org/10.1007/s10995-008-0375-8). [PubMed: 18566878].