Addiction Research & Therapy

Humbarger et al., J Addict Res Ther 2016, 7:1
http://dx.doi.org/10.4172/2155-6105.1000263

Research article Open Access

Childhood Health and Development in a Cohort of Infants Exposed Prenatally to Methadone or Buprenorphine

Olivia Humbarger[1], Daniel Galanto[2], Kelley Saia[3], Sarah M Bagley[4], Elisha M Wachman[5*] and Susan B Brogly[6]

[1]*Boston University School of Medicine, Boston, USA*

[2]*Department of Epidemiology, Boston University School of Public Health, Boston, USA*

[3]*Department of Obstetrics and Gynaecology, Boston Medical Centre, Boston, USA*

[4]*Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine, Boston, USA*

[5]*Division of Neonatology, Department of Paediatrics, Boston Medical Centre, Boston, USA*

[6]*Departments of Medicine and of Surgery, Queen's University, Kingston, ON, Canada*

[*]**Corresponding author:** Elisha Wachman, Division of Neonatology, Department of Paediatrics, Boston Medical Center, Boston, Tel: 617-414-3690; Fax: 617-414-7297; E-mail: Elisha.Wachman@bmc.org

Received date: Nov 26, 2015; **Accepted date:** Jan 22, 2016; **Published date:** Jan 29, 2016

Abstract

Background: Neonatal Abstinence Syndrome (NAS) due to in-utero opioid exposure is a growing problem with largely unknown long-term childhood outcomes. The objective of this study was to compare long-term outcomes of infants exposed to methadone versus buprenorphine in-utero.

Method: This retrospective cohort study included all pregnant women on buprenorphine or methadone and their infants born between 2006-2010 at our institution. Inpatient data was merged with outpatient data from 2006-2014 for those infants who continued to receive their paediatric care at our institution. We estimated unadjusted risk ratios (RR) of the following outcomes in buprenorphine versus methadone exposed infants: 1) routine healthcare visits, 2) growth and feeding disorders, 3) developmental delay, 4) visual problems, 5) hearing problems, 6) behavioural/attentional problems.

Results: Of 338 infants, 73.1% (N=247) continued to be followed at our hospital. The mean length of follow-up was 25.7 months (95% CI 22.9, 28.9). Infants in the buprenorphine group were less likely to be seen for hepatitis C exposure (19.6 vs. 9.2%, RR=0.60, 95% CI 0.40, 0.91) and more likely to have had a routine weight check (RR=2.14, 95% CI 1.05, 4.34). There were no differences in the incidence of developmental delay, ophthalmologic abnormalities, hearing deficits, or behavioural diagnoses between the groups. Results are limited by small sample size and lack of adjustment for confounders.

Conclusion: No significant differences in paediatric outcomes at 2 years of age after in-utero methadone or buprenorphine exposure were found, but the evidence is affected by study limitations. Further studies in a large patient population are warranted.

Keywords: Neonatal abstinence syndrome; NAS; Long-term outcomes; Opioid-exposed infants; Methadone; Buprenorphine

Abbreviations

NAS: Neonatal Abstinence Syndrome; Respect: Recovery Empowerment Social services Prenatal Care education community Treatment; i2b2: Informatics for Integrity Biology with the Bedside; BMC: Boston Medical Centre; RR: Risk Ratio; CI: Confidence Interval; DTO: Diluted Tincture of Opium

Introduction

There has been a sharp increase in the number of infants diagnosed with Neonatal Abstinence Syndrome (NAS) secondary to in-utero opioid exposure in the US [1]. NAS is a syndrome in which the infant experiences withdrawal symptoms such as neurologic irritability, autonomic dys-regulation, gastrointestinal and respiratory dysfunction as a result of abrupt cessation of exposure to maternal opioids or other medications [2]. The recommendation for pregnant women with opioid use disorder is treatment with methadone or buprenorphine agonist therapy, which has been associated with improved pregnancy and neonatal outcomes in comparison with continued illicit drug use [3]. All opioid exposed infants require hospitalization and monitoring for withdrawal signs after birth, and approximately 50-80% of these infants require pharmacologic therapy [3,4].

Short-term outcomes of methadone and buprenorphine exposed infants have been examined in cohort studies and randomized controlled trials; demonstrating buprenorphine was associated with improved maternal and neonatal outcomes [4-9]. Buprenorphine maintenance therapy is associated with a longer gestation, higher birth weight and length [5,7]. Some studies show a lower incidence of NAS with buprenorphine versus methadone exposure, with shorter duration of medication therapy for NAS and shorter hospitalizations [4-9]. Many of these studies, however, are limited by small sample size and insufficient control for confounding variables.

There is sparse evidence in regards to longer-term medical and neurodevelopmental outcomes in infants exposed to opioids in-utero. Visual deficits such as nystagmus, strabismus, and reduced visual acuity are reported to be higher among children exposed to opioids than the general population [10-12]. Studies of heroin or buprenorphine-exposed children have demonstrated delays in motor milestones, poor motor coordination, decreased attention span, and impaired verbal, reading, and arithmetic abilities compared with unexposed children [13,14]. Some studies comparing opioid-exposed to control children have found no differences in long-term neurodevelopmental outcomes [15,16]. Most long-term follow-up studies of opioid-exposed infants are relatively small and are confounded by concomitant maternal use of tobacco, other prescribed and un-prescribed substances, and many post-natal psychosocial risk factors [17]. Prior studies have not examined long term outcomes by prenatal exposure to buprenorphine versus methadone. The objective of this study was to examine longer term medical and developmental outcomes of infants prenatally exposed to opioid agonist therapy.

Methods

This was a retrospective cohort study of all pregnant women with opioid use disorders cared for through our Project RESPECT (Recovery-Empowerment-Social Services-Prenatal care-Education-Community Treatment) substance use prenatal clinic and their neonates delivered at Boston Medical Center (BMC) from June 2006 through December 2010. Project RESPECT provides comprehensive prenatal care, addiction counselling and treatment, social work services, and psychiatric care throughout the pregnancy and immediate postpartum period. RESPECT providers are able to prescribe buprenorphine, and work closely with local methadone clinics for women enrolled in RESPECT. This study was approved by the Boston University Medical Campus Institutional Review Board.

Data was abstracted from maternal and infant inpatient medical records, including details of maternal substance use disorder treatment, prescribed and illicit drug use, pregnancy and delivery information, birth outcomes, and details of infant NAS assessment and treatment. Exposure to illicit drugs was based on maternal report and confirmed with urine toxicology screening at every prenatal visit and at the time of delivery, and infant urine and meconium toxicology screens. The NAS treatment guidelines varied over the course of the study period. A modified Finnegan scoring tool was used for routine clinical care NAS assessments during the study period. This modified scale differs from the original Finnegan scale in the following ways: 1) tremors are given less weight, 2) addition of "restlessness" as a scoring item, 3) mottling is not included (Appendix).

Inpatient data for paediatric care after neonatal discharge was merged with outpatient medical record data from June 2006 to May 2014 to identify longer-term outcomes for infants who continued to receive paediatric follow-up care at BMC. Outpatient data was abstracted with use of ICD-9 codes using the BMC clinical data warehouse, which makes clinical data available for research, and the "Informatics for Integrity Biology with the Bedside" (i2b2) software, a platform that supports research and quality improvement work through a web-based query tool to allow for quick abstraction of clinical data from the electronic medical record based on specified search criteria. i2b2, an aggregate data query tool, is an established and validated database through the Boston University Clinical and Translational Science Institute [18]. For infants who continued to receive paediatric follow-up care at BMC, clinical data after neonatal discharge was categorized in to six different outcomes types: 1) routine healthcare and social visits, 2) growth and feeding disorders, 3) developmental delay, 4) vision problems, 5) hearing issues, and 6) behaviour/attention/sleep problems. The six major outcome types were defined prior to the i2b2 data query based on the most commonly identified medical problems from previous studies. After review of the data, the subcategories for outcome types were determined. The ICD-9 manual was used to clarify diagnoses into these six outcome categories and subcategories; each ICD-9 code was only classified into one subcategory.

Routine healthcare and social visits included well child visits, delayed immunizations, perinatal hepatitis C and HIV exposure follow-up, weight checks, psychosocial issues, housing issues, custody issues, family disturbances, or child abuse or neglect. Growth and feeding disorders included failure to thrive, weight loss or inadequate gain, obesity or overweight, feeding problems, short stature, excessive weight gain, or microcephaly. Developmental delay included general developmental delay, language delay, speech delay, motor delay, hypotonia, hypertonia, learning difficulties, or pervasive developmental disorder. Diagnoses of developmental delay were confirmed by direct chart review to determine age at assessment and assessment instrument used. Vision problems included strabismus, visual impairment, nystagmus, myopia, hypermetropia, and cataracts. Hearing issues included any hearing difficulties. Behaviour/attention/sleep problems included behaviour issues, attention issues, any sleep issue, seizures, staring spells, autism, or anxiety disorder. If a child did meet the above classifications, they were noted as being followed at our site but the additional medical diagnoses are not listed in our results.

Differences in maternal and child characteristics by 1) continued follow-up at our site and 2) prenatal buprenorphine versus methadone exposure were assessed using the Wilcoxon rank sum test for continuous outcomes and generalized linear models (log-link function) for the dichotomous outcomes. All analyses were conducted using SAS 9.3.

Results

During the study period, 338 infants prenatally exposed to opioid agonist therapy (332 pregnancies including 6 sets of twins) were delivered at our site. Differences in birth and NAS outcomes of infants followed and those who were not followed are shown in Table 1. Of the 338 infants, 73.1% (N=247, including 4 sets of twins) continued to be followed at BMC after neonatal discharge, of which 79.4% (N=196) were methadone and 20.6% (N=51) buprenorphine exposed. The mean length of follow up after neonatal discharge was 22.8 months (95% CI 17.0, 28.7 months) for buprenorphine exposed infants and 26.7 months (95% CI 23.2, 30.1 months) for methadone exposed infants. The corresponding mean number of paediatric follow up visits was 12.3 (95% CI 8.1, 16.5) and 14.9 (95% CI 12.7, 17.1) for buprenorphine and methadone exposed infants, respectively. Significantly more preterm versus term infants, and more methadone exposed infants continued to be followed (Table 1). The infants with on-going follow-up were less likely to have prenatal benzodiazepine exposure, and more likely to have been treated with phenobarbital for NAS.

Characteristic	No Follow-up (N=86)	Follow-Up (N=247)	Mean Difference (95% CI)	Relative Risk (95% CI)
Maternal Age (years) – Mean (Std)	27.5 (4.6)	27.9 (5.3)	-0.36 (-1.61, 0.90)	
Prenatal Care Initiated				
First Trimester – N (%)	35 (40.7)	121 (49.2)		0.83 (0.62, 1.10)
Second Trimester – N (%)	40 (46.5)	79 (32.1)		1.45 (1.08, 1.94)
Third Trimester – N (%)	0 (0)	0 (0)		
No Prenatal Care - N (%)	11 (12.8)	46 (18.7)		0.69 (0.37, 1.26)
In-Utero Primary Exposure				1.86 (1.29, 2.67)
Buprenorphine – N (%)	33 (38.4)	51 (20.6)	-1.87 (-5.41, 1.66)	
Mean Dose in mg (Std)	13.7 (8.9)	15.6 (7.5)		
Methadone – N (%)	53 (61.6)	196 (79.4)	9.81 (-5.72, 25.35)	
Mean Dose in mg (Std)	96.7 (53.1)	86.9 (37.9)		
In-Utero Co-Exposures				
Nicotine – N (%)	55 (78.6)	147 (84.0)		0.89 (0.71, 1.13)
Cocaine – N (%)	19 (22.9)	50 (21.4)		1.02 (0.87, 1.21)
Illicit opioids – N (%)	30 (36.1)	85 (36.3)		1.00 (0.87, 1.14)
SSRIs – N (%)	18 (20.9)	36 (14.6)		1.13 (0.93, 1.39
Benzodiazepines – N (%)	26 (30.2)	40 (16.2)		1.28 (1.04, 1.57)
Antipsychotics – N (%)	6 (7.0)	13 (5.3)		1.09 (0.80, 1.49)
C-section Delivery – N (%)	33 (38.4)	106 (42.9)		0.87 (0.60, 1.27)
Maternal Hepatitis C – N (%)	57 (79.2)	151 (83.0)		0.93 (0.75, 1.15)
Gestational Age at Birth, Weeks – Mean (Std)	38.6 (2.1)	38.2 (2.5)	0.40 (-0.19, 0.99)	
< 37 Weeks Gestational Age – N (%)	8 (9.3)	52 (21.1)		0.44 (0.22, 0.89)
Birth Weight, Grams – Mean (Std)	2862.6 (601.9)	2870.9 (629.4)	-8.32 (-162.3, 145.7)	
Pharmacologically Treated for NAS – N (%)	73 (84.9	210 (85.0)		1.00 (0.90, 1.11)
Length of Hospitalization, Days – Mean (Std)	21.2 (11.8)	23.1 (11.7)	-1.85 (-4.74, 1.04)	
NAS Medication Treatment				
Morphine – N (%)	37 (43.0)	111 (45.0)		-1.92 (-14.08, 10.25)
DTO – N (%)	36 (41.9	100 (40.5)		1.37 (-10.72, 13.47)
Phenobarbital – N(%)	1 (2.0)	61 (31.1)		-25.24 (-34.39, -16.09)
Clonidine – N(%)	2 (3.9)	5 (2.6)		1.37 (-4.40, 7.14)

Table 1: Maternal and neonatal characteristics by continued paediatric follow-up care at our hospital after neonatal discharge*, NAS = Neonatal Abstinence Syndrome; DTO=Diluted Tincture of Opium; SSRIs=Selective Serotonin Re-uptake Inhibitors; Std=Standard Deviation; CI =Confidence Interval,*: Unadjusted risk ratios, Missing data: Prenatal care (n=1); Hepatitis C (n=79).

Table 2 summarizes the long-term outcome data, grouped by methadone versus buprenorphine exposure. Fewer infants in the buprenorphine group were seen for perinatal Hepatitis C exposure (RR 0.60, 95% CI 0.40, 0.91) and more were seen for routine weight checks (RR 2.14, 95% CI 1.05, 4.34). No buprenorphine-exposed infants had a diagnosis of strabismus compared with 7.1% of methadone-exposed infants (non-significant). More buprenorphine exposed babies had a diagnosis of a sleep disorder (5.9% vs. 2.0%, RR=2.88, 95% CI 0.67, 12.47), though the confidence interval is wide. 17.8% of the study population had a diagnosis of development delay. The overall mean age

at diagnosis of developmental delay was 47 months (95% CI 41 months, 53 months). Of the 44 children with diagnoses of developmental delay, 61.4% of these diagnoses were confirmed with formal developmental testing by either a Massachusetts Early Intervention (EI) program (n=15) using the Battelle Developmental Inventory or the Mullen Scales of Early Learning, or the BMC Developmental and Behavioural Paediatrics clinic using the Mullen (n=12) with the remaining diagnoses (n=17) made by the primary care paediatrician after parental developmental skills interview and patient exam without use of a formal instrument. The mean age at testing with the Mullen scale was 29 months. Battelle and Mullen scores were not available in the electronic medical record. The six children with autism spectrum disorders were all diagnosed with the Autism Diagnostic Observation Schedule (ADOS-2). No striking difference was found in the risk of developmental delay in the buprenorphine and methadone groups.

Diagnosis Category	Buprenorphine (N=51) N (%)	Methadone (N=196) N (%)	Risk Ratio (95% CI)
Routine care / social Problems	35 (68.6)	150 (76.5)	0.90 (0.73, 1.10)
Well child visit	28 (54.9)	118 (60.2)	0.91 (0.69, 1.20)
Delayed immunizations	2 (3.9)	6 (3.1)	1.28 (0.27, 6.16)
Social Problems	7 (13.7)	37 (18.9)	0.73 (0.34, 1.53)
Hepatitis C Exposure	17 (33.3)	108 (55.1)	0.60 (0.40, 0.91)
Weight check	10 (19.6)	18 (9.2)	2.14 (1.05, 4.34)
Vaccination margin	4 (7.8)	21 (10.7)	0.73 (0.26, 2.04)
HIV Exposure	0 (0)	6 (3.1)	-
Growth and feeding diagnoses	12 (23.5)	46 (23.5)	1.00 (0.58, 1.75)
Failure to thrive	4 (7.8)	10 (5.1)	1.54 (0.50, 4.70)
Weight loss / inadequate gain	2 (3.9)	3 (1.5)	2.56 (0.44, 14.93)
Obesity / overweight	1 (2.0)	12 (6.1)	0.32 (0.04, 2.41)
Feeding problem	3 (5.9)	10 (5.1)	1.15 (0.33, 4.04)
Short stature	0 (0)	5 (2.6)	-
Weight gain	4 (7.9)	20 (10.2)	0.77 (0.27, 2.15)
Microcephaly	0 (0)	5 (2.6)	-
Developmental delay diagnoses	6 (11.8)	38 (19.4)	0.61 (0.27, 1.36)
General delay, unspecified	1 (2.0)	17 (8.7)	0.23 (0.03, 1.66)
Language Delay / Speech problems	6 (11.8)	25 (12.8)	0.92 (0.40, 2.13)
Motor Delay	0 (0)	0 (0)	-
Hypotonia	1 (2.0)	2 (1.0)	1.92 (0.18, 20.77)
Hypertonia	0 (0)	5 (2.6)	-
Learning difficulties	0 (0)	2 (1.0)	-
Pervasive developmental disorder	0 (0)	0 (0)	-
Visual diagnoses	2 (3.9)	22 (11.2)	0.35 (0.08, 1.44)
Strabismus	0 (0)	14 (7.1)	-
Visual impairment	2 (3.9)	4 (2.0)	1.92 (0.36, 10.20)
Nystagmus	0 (0)	2 (1.0)	-

Other visual diagnosis	0 (0)	4 (2.0)	-
Hearing diagnoses	0 (0)	4 (2.0)	-
Behaviour/Attention /Sleep	4 (7.8)	22 (11.2)	0.70 (0.25, 1.94)
Behavioural problems	1 (2.0)	10 (5.1)	0.38 (0.05, 2.93)
Attentional problems	0 (0)	2 (1.0)	-
Sleep disorders	3 (5.9)	4 (2.0)	2.88 (0.67, 12.47)
Seizures / staring spells	1 (2.0)	2 (1.0)	1.92 (0.18, 20.77)
Autism	0 (0)	6 (3.1)	-
Anxiety disorder	0 (0)	3 (1.5)	-

Table 2: Infant clinical events by in-utero exposure to prenatal opioid agonist treatment.

Discussion

This retrospective cohort study is the first to compare longer term outcomes following prenatal exposure to methadone or buprenorphine. Prior studies which look at the short-term outcomes of methadone versus buprenorphine exposed infants have shown advantages for the buprenorphine group. In our study, which followed children out to an average of 2 years of age, we did not see any striking differences in long-term outcomes between the two exposure groups. However, our evidence is limited by the small sample size, lack of adjustment for confounders and potential for selection bias as not all infants continued to be followed at our site.

Some prior studies have suggested lower rates of delayed motor, social, and language development prenatal opioid exposure with buprenorphine vs. methadone [19-21]. Our study also suggested a lower rate in the buprenorphine group, although causal effects cannot be implicated due to potential systematic error and the large amount of random error. We also identified a 7.1% rate of strabismus in the methadone-exposed infants in our cohort. Previous studies have also identified higher rates of strabismus with opioid exposure, particularly methadone, relative to the general paediatric population [22,23]. However, this could be confounded by concomitant exposure to cocaine, tobacco, and alcohol, which are also associated with higher rates of strabismus [24]. Opioid exposure also predisposes to prematurity and low birth weight, both of which are independent risk factors for strabismus.

This study has a number of limitations. The choice of opioid agonist therapy depended upon the characteristics of the mother at the time of presentation for care; women at higher risk of poor pregnancy outcomes were likely treated with methadone versus buprenorphine [5]. Because of our small study size, results are unadjusted for any confounders. Second, our study population was restricted to children that continued to be followed at our site, with more methadone exposed children continued to be followed. Children that continued to be followed may have had higher comorbidity and thus selection bias may account for our observed findings. Specifically, those with developmental delays were followed for a longer period of time. Finally, this study is limited by its use of ICD-9 codes and problem lists to determine the incidence of diagnoses. The consistency of ICD-9 coding depends on the quality of communication between the child's guardians and the clinicians for symptoms, the clinician's description of the child's condition in the medical records. For those children with developmental delays, additional chart review was performed to confirm the diagnoses; however standardized instruments were used in only 61.4% of cases. All families in this study participated in Project RESPECT prenatally and in the immediate postpartum period. Project RESPECT is a unique program that provides in addition to prenatal care, addiction counselling, social work services, and psychiatric care for these women with opioid use disorders. There are systematic differences between comprehensive supportive programs such as RESPECT and solely receiving methadone or buprenorphine prescription from a provider. This may have affected follow-up rates, infant outcomes, and may limit the generalizability of our results to other settings.

Methadone or buprenorphine are recommended in opioid use disorder in pregnancy to provide stability while engaging women in therapy to reduce the risk of relapse, and reducing perinatal complications. Our study is novel in that we compared long-term outcomes in methadone versus buprenorphine exposed infants and found no significant differences in outcomes at 2 years of age. Our results, however, are preliminary and should be investigated in larger prospective studies.

Acknowledgement

We would like to thank the Boston University School of Medicine's Summer Research Program, and Linda Rosen from the Boston Medical Center Clinical Data Warehouse for her assistance with data preparation for this project. Thank you also to the Boston University Medical Centre Perinatal Substance Use research group for their contribution. Research in this publication was supported by the Boston University School of Public Health Pilot Fund (S Brogly) and the Boston University School of Medicine Summer Research Program (O Humbarger).

References

1. Patrick SW, Davis MM, Lehman CU, Cooper WO (2015) Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. J Perinatol 35: 667.
2. Jansson LM, Velez M (2012) Neonatal abstinence syndrome. Curr Opin Pediatr 24: 252-258.
3. Welle-Strand GK, Skurtveit S, Jones HE, Waal H, Bakstad B, et al. (2013) Neonatal outcomes following in utero exposure to methadone or

buprenorphine: A National Cohort Study of opioid-agonist treatment of Pregnant Women in Norway from 1996 to 2009. Drug Alcohol Depend 127: 200-206.

4. Jones HE, Kaltenbach K, Heil SH, Stine SM, Coyle MG, et al. (2010) Neonatal abstinence syndrome after methadone or buprenorphine exposure. N Engl J Med 363: 2320-2331.
5. Brogly SB, Saia KA, Walley AY, Du HM, Sebastiani P (2014) Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis. Am J Epidemiol 180: 673-686.
6. Metz V, Jagsch R, Ebner N, Würzl J, Pribasnig A, et al. (2011) Impact of treatment approach on maternal and neonatal outcome in pregnant opioid-maintained women. Hum Psychopharmacol 26: 412-421.
7. Kakko J, Heilig M, Sarman I (2008) Buprenorphine and methadone treatment of opiate dependence during pregnancy: Comparison of fetal growth and neonatal outcomes in two consecutive case series. Drug Alcohol Depend 96: 69-78.
8. Welle-Strand GK, Skurtveit S, Jones HE, Waal H, Bakstad B, et al. (2013) Neonatal outcomes following in utero exposure to methadone or buprenorphine: a National Cohort Study of opioid-agonist treatment of Pregnant Women in Norway from 1996 to 2009. Drug Alcohol Depend 127: 200-206.
9. Lacroix I, Berrebi A, Garipuy D, Schmitt L, Hammou Y, et al. (2011) Buprenorphine versus methadone in pregnant opioid-dependent women: A prospective multicenter study. Eur J Clin Pharmacol 67: 1053-1059.
10. Hunt RW, Tzioumi D, Collins E, Jeffery HE (2008) Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. Early Hum Dev 84: 29-35.
11. Gupta M, Mulvihill AO, Lascaratos G, Fleck BW, George ND (2012) Nystagmus and reduced visual acuity secondary to drug exposure in utero: Long-term follow-up. J Pediatr Ophthalmol Strabismus 49: 58-63.
12. Spiteri Cornish K, Hrabovsky M, Scott NW, Myerscough E, Reddy AR (2013) The short- and long-term effects on the visual system of children following exposure to maternal substance misuse in pregnancy. Am J Ophthalmol 156: 190-194.
13. Ornoy A, Segal J, Bar-Hamburger R, Greenbaum C (2001) Developmental outcome of school-age children born to mothers with heroin dependency: Importance of environmental factors. Dev Med Child Neurol 43: 668-675.
14. Wahlsten VS, Sarman I (2013) Neurobehavioural development of preschool-age children born to addicted mothers given opiate maintenance treatment with buprenorphine during pregnancy. Acta Paediatr 102: 544-549.
15. Kaltenbach K, Finnegan LP (1987) Perinatal and developmental outcome of infants exposed to methadone in-utero. Neurotoxicol Teratol 9: 311-313.
16. Kaltenbach K, Finnegan LP (1984) Developmental outcome of children born to methadone maintained women: a review of longitudinal studies. Neurobehav Toxicol Teratol 6: 271-275.
17. Messinger DS, Bauer CR, Das A, Seifer R, Lester BM, et al. (2004) The maternal lifestyle study: cognitive, motor, and behavioral outcomes of cocaine-exposed and opiate-exposed infants through three years of age. Pediatrics 113: 1677-1685.
18. Boston University i2b2 Software (2016).
19. McGlone L, Mactier H (2015) Infants of opioid-dependent mothers: neurodevelopment at six months. Early Hum Dev 91: 19-21.
20. Beckwith AM, Burke SA (2015) Identification of early developmental deficits in infants with prenatal heroin, methadone, and other opioid exposure. Clin Pediatr (Phila) 54: 328-335.
21. Logan BA, Brown MS, Hayes MJ (2013) Neonatal abstinence syndrome: treatment and pediatric outcomes. Clin Obstet Gynecol 56: 186-192.
22. Gill AC, Oei J, Lewis NL, Younan N, Kennedy I, et al. (2003) Strabismus in infants of opiate-dependent mothers. Acta Paediatr 92: 379-385.
23. Nelson LB, Ehrlich S, Calhoun JH, Matteucci T, Finnegan LP (1987) Occurrence of strabismus in infants born to drug-dependent women. Am J Dis Child 141: 175-178.
24. Dominguez R, Aguirre Vila-Coro A, Slopis JM, Bohan TP (1991) Brain and ocular abnormalities in infants with in utero exposure to cocaine and other street drugs. Behavioural Am J Dis Child 145: 688-695.