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

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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

There is sparse evidence in regards to longer-term medical and neurodevelopmental outcomes in infants exposed to opioids in-utero. Visual defcits 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 diferences 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

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)

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.

Other visual diagnosis	0 (0)	4 (2.0)	-

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