



# Infants of opioid-dependent mothers: Neurodevelopment at six months



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## ABSTRACT

**Objective:** The aim of this study is to describe infant neurodevelopment in 81 infants of methadone-prescribed opioid-dependent mothers.

**Methods:** Griffith MD scores at six months.

**Results:** Scores were lower in all domains compared to controls ( $p < 0.001$ ). Poly-drug exposed infants and those treated for neonatal abstinence syndrome performed significantly poorer ( $p = 0.002$  and  $p = 0.008$  respectively).

**Conclusions:** Infants of methadone-maintained opioid-dependent mothers show poorer neurodevelopment at six months of age than non-drug exposed comparison infants. Developmental difficulties are confounded by delayed visual development.

**Practice implications:** These highly vulnerable children merit close surveillance throughout infancy.

**Summary:** Griffith MD scores at six months in 81 infants born to methadone-prescribed opioid-dependent mothers were lower in all domains compared to controls ( $p < 0.001$ ). Poly-drug exposed infants and those treated for neonatal abstinence syndrome performed significantly poorer ( $p = 0.002$  and  $p = 0.008$  respectively). Co-existing visual problems were common.

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## 1. Introduction

Many publications have reported adverse neurodevelopmental outcomes for infants born to drug-misusing mothers, but the majority of studies have been small and confounded by social factors and low rates of follow-up, with few data regarding *in utero* drug exposure and neonatal behavior [1,2]. Babies born to methadone-prescribed opioid-dependent mothers have reduced occipito-frontal head circumference (OFC) at birth relative to controls matched for gestation, socio-demographics and maternal smoking [3] although head growth appears to catch up in the first year of life [1]. Recent evidence indicates an association between maternal drug misuse during pregnancy and impaired infant visuo-cortical development, with abnormalities persisting at least to mid childhood [4,5].

We have previously described abnormal clinical and electrophysiological visual function at six months of age in infants born to opioid-dependent women prescribed maintenance methadone in pregnancy [4]: we now present neurodevelopmental outcomes at six months.

## 2. Methods

This was a prospective cohort study conducted in a large inner-city maternity unit in Glasgow. Infants of opioid-dependent mothers

prescribed maintenance methadone during pregnancy were recruited within three days of birth; exclusion criteria included birth before 36 weeks' gestation, congenital ocular abnormality and significant neonatal illness. For comparative purposes, 50 healthy, non-maternal drug-exposed infants were recruited from the same hospital, matched for gestation, birth weight and maternal postcode at delivery. Data collected included development of neonatal abstinence syndrome (NAS) requiring pharmacological treatment; this was commenced as indicated according to local protocol, with oral morphine as first line treatment and phenobarbital as second line treatment. Visual evoked potentials were measured within the first three days of life and are described in an earlier manuscript [6]. Ethics approval was obtained and all mothers gave written informed consent. Infants were invited to re-attend at six months of age and transportation provided as required to facilitate this visit.

### 2.1. Drug exposure

A confidential maternal interview was conducted immediately after study recruitment regarding drug use during pregnancy. All interviews were conducted by one investigator (LMcG). Maternal urine samples were collected at the hospital booking visit and, if additional illicit drug use suspected, at subsequent antenatal appointments. A specimen of infant urine and a sample of meconium were obtained as soon as possible after consent for inclusion in the study. Urine was analyzed using enzyme multiplied immunoassay technique assays run to Substance Abuse and Mental Health Services Administration guidelines.

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Meconium samples were subject to ELISA screening followed by GC-MS and LC-MS-MS for selected positives. Any positive result from toxicology or maternal interview defined *in utero* drug exposure. Infants were classified into five drug exposure groups: group 1 = opiates alone, group 2 = opiates + cannabis, group 3 = opiates + benzodiazepines, group 4 = opiates + benzodiazepines + cannabis, and group 5 = opiates + other drugs including stimulants. When sufficient meconium was obtained, samples were also analyzed for fatty acid ethyl esters (FAEEs). A cut off value of >10,000 ng/g of meconium was considered indicative of excess alcohol consumption in pregnancy [7].

## 2.2. Six month assessment

Neurodevelopmental assessment was undertaken using the Griffiths Mental Development Scales for babies 0 to 2 years (1996 revision). All assessments were undertaken by one person (LMcG), in the presence of an optometrist blinded to the infant's drug exposure group.

## 2.3. Statistics

As developmental score data were skewed, comparisons between groups were made with Mann-Whitney tests and between sub-groups with Kruskal-Wallis tests. Linear regression models corrected for potential confounders.

## 3. Results

107 infants were brought for follow up assessment: 81 of 102 (79%) drug-exposed and 26 of 50 (52%) comparison infants originally recruited. Median age at follow-up was 27 weeks (IQR 26–28) for both groups. Comparison infants had larger OFC at birth (mean 34.1 +/- (SD)1.6 cm versus 33.5 +/- 1.56 cm;  $p = 0.015$ ) but there was no significant difference between the groups at six months (mean OFC 43.83 +/- (SD)1.88 versus 43.26 +/- 1.54 cm). Comparison infants tended to be heavier at six months (mean 7520 +/- (SD)1050 g versus 7940 +/- 1090 g), consistent with a tendency to heavier birth weight (mean 3005 +/- (SD)539 g and 2892 +/- 505 g respectively) but neither of these differences was significant. Infants who did not attend follow-up did not differ with regard to their birth weight, OFC, gestation, Apgar score or postcode.

### 3.1. Drug and alcohol exposure

The majority of infants had been exposed to illicit drugs *in utero* in addition to prescribed methadone, including opiates (75%), benzodiazepines (67%), cannabis (64%) and stimulants (26%). There were 12, 12, 11, 25 and 21 infants in exposure groups 1, 2, 3, 4 and 5 respectively. Only 8 infants had no evidence of exposure to any drugs other than methadone. 39 babies received oral morphine for treatment of NAS, of whom 15 were additionally treated with phenobarbital. Twenty one drug-exposed (43% of the 49 tested) and three comparison infants (17% of the 18 tested) had elevated FAEEs in meconium, in none of whom was fetal alcohol syndrome suspected.

### 3.2. Developmental assessment

Eight (9.9%) drug-exposed infants scored <85 on Griffiths assessment. All comparison infants scored  $\geq 95$  ( $p = 0.003$ ). Drug-exposed infants performed poorer than comparison infants in all sub-scales, even after correcting for maternal smoking and known excess alcohol consumption in pregnancy as determined by meconium analysis (Table 1). Six of the 8 drug-exposed infants who scored <85 had one or more co-existing visual problems, including reduced visual acuity in all cases. Visual impairment was independently associated with adverse neurodevelopmental outcome as defined by GQ <85 ( $p < 0.001$ ). There was no correlation between prescribed maternal methadone dose

at delivery and GQ score. Infants who received any pharmacological treatment for NAS performed significantly poorer than infants who did not require treatment (median GQ 95 (IQR 91 to 99) versus 99 (IQR 94 to 102);  $p = 0.008$ ). Development was poorer in those infants exposed to multiple illicit drugs *in utero*, with most marked differences in locomotor and hand-eye skills ( $p = 0.002$ ) (Table 2). Accommodated infants ( $N = 20$ ) performed poorer than those infants still in the care of their birth parent(s) ( $N = 61$ ) (median GQ 92 versus 97,  $p = 0.003$ ). However, the former were more likely to have been treated for NAS ( $p = 0.039$ ) and to have had poly-drug exposure *in utero* ( $p = 0.015$ ).

## 4. Discussion

At six months of age infants born to methadone-maintained opioid-dependent mothers had lower developmental scores in all areas compared to infants matched for gestation, birth weight and postcode at delivery. We have previously reported that 40% of the drug-exposed cohort failed visual assessment at six months [4]; these additional data lend weight to concerns regarding longer term outcome for children of opioid-dependent mothers [1,2,4,5]. All infants who scored <85 were born to opioid-dependent mothers; three quarters of these eight infants had reduced visual acuity with or without other visual problems including strabismus and nystagmus. Differences in neurodevelopment persisted after correcting for smoking and measured excess alcohol consumption during pregnancy.

Infants who received pharmacological treatment for NAS had lower GQ scores at six months than those who demonstrated less severe (or no) NAS; it is impossible to ascertain from the relatively small numbers of affected babies if the process of NAS itself, medication (morphine +/- phenobarbital) or prolonged hospitalization (perhaps with secondary adverse effects upon parenting), or a combination of these factors accounts for this finding. The majority of infants were exposed *in utero* to some illicit drugs in addition to maintenance methadone [8]; across all areas of development those infants exposed to multiple illicit drugs *in utero* performed poorer than infants exposed to opiates alone, with most marked differences in locomotor performance. Poly-drug exposure may account for lower GQ scores among accommodated infants, but accommodated infants were also more likely to have been treated for NAS.

Differences in OFC at birth [6] between drug-exposed and comparison infants were no longer significant at six months, consistent with the findings of Hunt *et al.* [1], and suggestive of a temporary adverse effect upon fetal head growth. This could be due to illicit drugs, prescribed methadone and/or other factors associated with drug misuse.

Strengths of this prospective study include large sample size, high rates of follow-up among the drug-exposed babies, and a comparison group matched for gestation and area of residence. All assessments were carried out by one person, ensuring consistency of practice and using a well validated developmental tool. We acknowledge that postcode at delivery is not an ideal proxy for social deprivation, and that other factors including parenting skills and maternal nutrition undoubtedly influence infant neurodevelopmental outcome, but such factors are

**Table 1**  
Developmental scores for drug-exposed and comparison infants.

Development	Maternal drug-exposed infants ( $n = 81$ )	Comparisons ( $n = 26$ )	$p$ -value	Adjusted $p$ -value
Locomotor	102 (93–107)	111 (101–111)	<0.001	0.006
Personal-social	94 (88–96)	99 (94–103)	<0.001	0.001
Language-hearing	105 (105–109)	109 (105–109)	<0.001	0.007
Eye-hand	94 (86–99)	104 (99–104)	<0.001	0.001
Performance	96 (86–100)	101 (101–111)	<0.001	0.002
<b>GQ</b>	<b>97 (93–100)</b>	<b>105 (101–108)</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>

Data are medians (inter-quartile ranges). Statistical analysis was done using Mann-Whitney tests. Adjusted  $p$ -values were after correcting for maternal smoking status and excess alcohol intake during pregnancy using linear regression models.

**Table 2**  
Developmental scores and drug exposure group.

Development	Drug exposure group					p-value
	1	2	3	4	5	
Locomotor	104.5 (98–118)	102.0 (95–107)	102.0 (98–107)	98.0 (93–102)	93.0 (84–102)	0.020
Personal–social	96.5 (94–103)	94.0 (90–98)	94.0 (89–94)	89.0 (84–94)	89.0 (84–97)	0.062
Language	107.0 (101–109)	109.0 (105–109)	105.0 (105–109)	105.0 (105–105)	105.0 (98–105)	0.115
Eye–hand	94.0 (94–99)	99.0 (94–104)	94.0 (89–99)	94.0 (82–99)	94.0 (84–97)	0.039
Performance	96.0 (91–101)	96.0 (91–101)	96.0 (91–101)	96.0 (86–96)	91.0 (82–96)	0.092
<b>GQ</b>	<b>100</b> (97–103)	<b>99.5</b> (98–103)	<b>99.0</b> (94–100)	<b>95.0</b> (93–97)	<b>93.0</b> (89–98)	<b>0.002</b>

Data are medians with inter-quartile ranges given in brackets below. Statistical tests were done using Kruskal–Wallis tests.

extremely difficult to quantify. Although there was a higher loss to follow-up of comparison infants, there were no significant differences in demographic characteristics between those comparison infants who did or did not attend for follow-up.

Further unique strengths of this study are the detailed data regarding *in utero* drug exposure and consistent description of NAS. Additionally, objective assessment of excess *in utero* alcohol exposure in a substantial proportion allowed partial correction for the confounding effects of *in utero* alcohol exposure on developmental outcomes. Almost certainly poly-drug use and excessive alcohol consumption are under-reported in the majority of studies describing outcomes for drug-misusing pregnancies; objective measures to quantify these important confounders should be considered in future studies.

## 5. Conclusions

Infants of methadone-maintained opioid-dependent mothers show poorer neurodevelopment at six months of age than non-drug exposed comparison infants, which is not explained by cigarette smoking or excessive alcohol consumption during pregnancy. Poly-drug exposed infants and those infants who develop significant NAS are at higher risk, and developmental difficulties are confounded by delayed visual development.

## Contributions

LMcG was involved in study design, recruited subjects and carried out assessments at six months. She wrote the first draft of the manuscript and approved the final version. HM conceived the study, and extensively edited the manuscript before approving the final version.

## Conflict of interest statement

The authors declare no conflict of interest in the preparation of this manuscript.

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