study design, recruited all patients, collected and analyzed data, and drafted the manuscript; Drs Hamilton and Bradnam developed the original idea; Drs Hamilton and McCulloch made substantial contribution to study design and analysis of data; Mr Boulton contributed to study design and collection and analysis of data; Dr Bradnam made substantial contribution to study design; Dr Weaver contributed to study design; Dr Mactier made substantial contribution to study design and execution of study; Drs Hamilton, McCulloch, Bradnam, Weaver, and Mactier and Mr Boulton revised the manuscript critically for important intellectual content; and all authors approved the final version of the manuscript.

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Address correspondence to Laura McGlone, MBChB, MRCPCH, Royal Hospital for Sick Children, Dalmarnock, Glasgow, Scotland, G3 8SR. E-mail: lauramcglone@doctors.org.uk

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abstract

**OBJECTIVE:** Drug misuse in pregnancy is associated with impaired infant visual development. Pilot data showed abnormal flash visual evoked potentials (VEPs) in neonates exposed to methadone in utero, but results were confounded by intrauterine growth restriction, gestation, and ongoing drug misuse. This large cohort study aimed to clarify the effects on neonatal flash VEPs of maternal drug misuse in pregnancy, including prescription of substitute methadone and subsequent development of neonatal abstinence syndrome.

**METHODS:** This was a prospective cohort study. Flash VEPs were recorded within 3 days of birth from 100 healthy infants of drug-misusing mothers prescribed substitute methadone during pregnancy and 50 comparison infants matched for birth weight, gestation, and socioeconomic deprivation. VEP morphology was classified as mature, typical, or immature, and amplitudes and implicit times of the major waveform components measured. Drug exposure was determined by maternal history, maternal and infant urine, and meconium toxicology.

**RESULTS:** VEPs from maternal drug-exposed infants were more likely to be of immature waveform (P < .001) and were smaller in overall amplitude (median 27 μV vs 39 μV, P < .001) compared with non-drug-exposed infants. Most infants were exposed to illicit drugs in addition to prescribed methadone; differences in VEP parameters were independently associated with maternal prescribed methadone and persisted after correcting for birth weight, cigarette smoking, and excess in utero alcohol exposure.

**CONCLUSIONS:** In utero exposure to prescribed substitute methadone is associated with altered flash VEPs in the newborn period and these infants may warrant early clinical visual assessment. *Pediatrics* 2013;131:e857–e863
Maternal drug misuse is a significant social problem affecting an estimated 250,000 to 350,000 children in the United Kingdom. Management of maternal opiate misuse in pregnancy includes substitute prescribing of methadone, a synthetic opioid that stabilizes lifestyle, lessens risk-taking behavior, and reduces the incidence of preterm birth and intrauterine growth restriction (IUGR). Methadone use in pregnancy is associated with improved compliance with antenatal care, but most mothers also misuse other substances, particularly opiates and benzodiazepines. There is increasing evidence to suggest that maternal drug misuse in pregnancy has adverse effects on infant visual development, with reported abnormalities, including reduced visual acuity, nystagmus, delayed visual maturation, strabismus, and refractive errors. Flash visual evoked potentials (VEPs) in infancy reflect the integrity and maturity of the visual system, and we have demonstrated abnormal VEPs in newborn infants exposed to methadone in utero. That pilot study was, however, limited by small numbers and confounded by poly-drug exposure and IUGR. Abnormal infant flash VEPs in other high-risk neonatal groups have been linked with long-term visual, motor, and learning disabilities. The aims of the current study were to investigate the effects of maternal drug misuse on neonatal visual development and to assess any relationship between early visual electrophysiology and subsequent neonatal abstinence syndrome (NAS).

METHODS

This prospective cohort study was conducted at the Princess Royal Maternity in Glasgow, UK. Eligible infants were born to drug-misusing mothers prescribed substitute methadone during pregnancy. Exclusion criteria were birth before 36 completed weeks’ gestation, congenital ocular abnormality, and significant neonatal illness. Infants <36 weeks’ gestation were excluded to remove the potential confounding effect of preterm birth on the neonatal VEP waveform. For comparative purposes, healthy, non-drug-exposed infants were recruited within the same maternity unit. To correct for potential confounding factors, comparison infants were matched for completed week of gestation, birth weight ± 250 g, and Carstairs deprivation index score ± 1 (deprivation category based on the presence of overcrowding, unemployment, social class, and car ownership). Ethics approval was granted by the West of Scotland Research Ethics Committee, and written informed parental consent was obtained for all participants.

Sample Size

A pilot study demonstrated differences in flash VEP morphology, amplitude, and implicit times of the major components between 21 methadone-exposed infants and 20 control infants. Local audit suggested that ~20% of pregnant women prescribed substitute methadone used no additional illicit substances and so 100 maternal drug-exposed infants were expected to include a subgroup of 20 who had been exposed to methadone alone. Approximately 50% of infants were predicted to develop significant NAS. A group of this size (n = 50) was likely to have 95% confidence intervals (CIs) of the mean for flash VEP P2 amplitude of ±2 μV and for P2 implicit time of ±11 ms, which is adequately narrow for clinical purposes.

Clinical Data Collection

Maternal and infant demographic characteristics were collected at study enrollment and the severity of NAS recorded from the case notes. The latter was classified by using a modified Lipsitz score: 1 = no NAS, 2 = mild NAS (no pharmacological treatment required), 3 = moderate NAS (standard oral morphine treatment), and 4 = severe NAS (escalated treatment with phenobarbital).

Drug Exposure and Toxicology

After study recruitment, a confidential interview was conducted with all mothers regarding drug and alcohol use during pregnancy. Maternal urine samples were collected routinely at the hospital booking visit and specimens of the infant’s urine and meconium were obtained as soon as possible after delivery. Urine samples were analyzed by the regional toxicology laboratory by using the enzyme multiplied immunoassay technique assays run to Substance Abuse and Mental Health Services Administration guidelines on an Abbott Architect Analyzer (Abbott, Abbott Park, IL). Assays included methadone, opiates, benzodiazepines, amphetamines, cannabinoids, and cocaine metabolites. Meconium samples were screened for the same drugs by using enzyme linked immunosassay technique assays run to Substance Abuse and Mental Health Services Administration guidelines on an Abbott Architect Analyzer (Abbott, Abbott Park, IL). Assays included methadone, opiates, benzodiazepines, amphetamines, cannabinoids, and cocaine metabolites. Meconium samples were also analyzed for fatty acid ethyl esters (FAEES) to identify infants exposed to excess alcohol in utero by using liquid chromatography–mass spectrometry. A cutoff value of >10,000 ng/g of meconium was used to signify excess alcohol consumption in pregnancy. Meconium samples were collected from control infants.
and analyzed for drugs of misuse and FAEEs.

**Neonatal VEP Recording**

Flash VEPs were recorded within the first 72 hours of life from an active midline occipital electrode over the visual cortex at Oz, with a midline frontal reference electrode at Fz, according to international standards.^{21,22} Stimulus generation, recording, and data storage were carried out by using an Espion evoked potential system (Diagnosys LLC, Lowell, MA) and flashes delivered by using a hand-held light-emitting diode stimulator to deliver a white pulse flash with time-integrated luminance of 28 cd.s.m^{−2} at a frequency of 1 Hz. Impedance was <10 kohms, recorded at the start and end of each recording. A minimum of 30 trials per average were recorded and the procedure repeated to check reproducibility. Each VEP recording session took ∼30 minutes to complete. All VEPs were recorded before commencement of any pharmacological treatment of NAS.

**Data Analysis**

Flash VEPs were categorized as present or absent. When present, the amplitude and implicit times of peaks and troughs were measured. Peaks and troughs were defined as follows: P1 = any positive component before P2; P2 = the major positive component between 126 and 300 ms and preceding N3 if present; N3 = negative component between 200 and 400 ms; P3 = positive component after the N3. The total summed amplitude of all peaks and troughs was calculated. Each flash VEP was also categorized by waveform morphology, based on normal maturation of VEP morphology in infants from preterm to early postterm.^{15–17} Descriptive categories were: typical (predominant positivity near 200 ms [P2], no P1 present), mature (P1 and P2 present), immature (predominant negativity near 300 ms [N3] with either no detectable P2 or with P2 amplitude less than one-third of the N3 amplitude), and atypical (reproducible VEP with an unusual waveform that did not meet criteria of other categories) (Fig 1).^{17} All VEPs were assessed by 2 observers,
of whom was blinded to the infant’s group and clinical course.

**Statistics**

VEP implicit times and amplitudes were tested for normality by using Anderson-Darling tests; as the data were of skewed distribution, comparisons between groups were done by using Mann-Whitney tests and Kruskal-Wallis tests. VEP morphology was compared between groups by using χ² tests. Linear and logistic regression models were used to correct for potential confounders and to assess the effects of independent drugs of misuse on neonatal flash VEPs.

**RESULTS**

One hundred maternal methadone-exposed infants (98% of eligible infants approached) and 50 matched comparison infants were recruited. Sixteen methadone-exposed infants were excluded because of preterm birth (n = 11) or significant illness (n = 5). Maternal and infant demographic characteristics are shown in Table 1. Although birth weights were comparable, maternal methadone-exposed infants had smaller occipitofrontal head circumferences (33.5 cm vs 34.1 cm, 2-sample t-test P = .015). Substitute methadone-prescribed mothers were more likely to report cigarette smoking (95% vs 60%, χ² test P < .001) (Table 1).

The most commonly misused drugs in addition to methadone were opiates (74%), benzodiazepines (66%), and cannabis (62%) (Table 2, Fig 2). Only 9 infants were exposed to methadone alone (Fig 2); a further 8 were additionally exposed to other opiates giving a subgroup of 17 exposed to opiates alone. Meconium toxicology analysis was performed on 30 of the comparison infants, 3 of whom tested positive for cannabinoids. Of those infants whose meconium sample was sufficient to test for FAEEs, 26 drug-exposed (26/63, 41%) and 5 comparison infants (5/21, 23%) had elevated levels, indicative of excess alcohol exposure in utero. Fourteen drug misusing mothers were taking prescribed antidepressant and/or antipsychotic medication during pregnancy, compared with none of the comparison mothers. To investigate any potential confounding effect of these maternal prescribed drugs on the newborn infant, VEP and VEP parameters were compared between drug-exposed infants whose mothers were taking prescribed antidepressant medication and those who were not. There was no difference in VEP amplitude, implicit time, or morphology between these groups.

**Comparison of Flash VEPs**

Methadone-exposed infants were less likely to demonstrate P1 and N2 components than comparison infants (P1: 21% vs 48%, χ² = 11.6, P = .001; N2: 38% vs 60%, χ² = 6.5, P = .011) and had VEPs of smaller total amplitude: 27 μV (interquartile range 17–42) vs 39 μV (interquartile range 28–67) (Mann-Whitney test P < .001, 95% CI –20 to –6) (Table 3). Overall, maternal methadone-exposed infants had more

---

**Table 1** Demographic Characteristics of Infants and Mothers

<table>
<thead>
<tr>
<th>Case (n = 100)</th>
<th>Comparison (n = 50)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender,b % male</td>
<td>46</td>
<td>44</td>
</tr>
<tr>
<td>Mode of delivery,c %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVD</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>LUSCS</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Instrumental</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Gestation, wk</td>
<td>39.3 (38.2–40.1)</td>
<td>39.7 (38.1–41.6)</td>
</tr>
<tr>
<td>Birth weight</td>
<td>2982 (± 503)</td>
<td>3005 (± 539)</td>
</tr>
<tr>
<td>SGA, %</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>LBW, %</td>
<td>20</td>
<td>18</td>
</tr>
<tr>
<td>OFC,c cm</td>
<td>33.5 (± 1.56)</td>
<td>34.1 (± 1.6)</td>
</tr>
<tr>
<td>Microcephaly,c %</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Feeding at D/C,c %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottle</td>
<td>87</td>
<td>90</td>
</tr>
<tr>
<td>Breast</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Mixed</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Maternal smoking,b %</td>
<td>95</td>
<td>60</td>
</tr>
<tr>
<td>Maternal BMI</td>
<td>23 (21–26)</td>
<td>23.5 (21–30)</td>
</tr>
<tr>
<td>Maternal DEPCAT</td>
<td>7 (5–7)</td>
<td>6 (4–7)</td>
</tr>
</tbody>
</table>

<p>| TABLE 2 Drug Exposure: Comparison of History and Toxicology (Cases) |
|---------------------|---------------------|---------------------|</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>History (n = 100)</th>
<th>Maternal Urine (n = 84)</th>
<th>Infant Urine (n = 70)</th>
<th>Meconium (n = 74)</th>
<th>Combined (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone, %</td>
<td>100</td>
<td>92</td>
<td>61</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>Other opiates, %</td>
<td>54</td>
<td>56</td>
<td>36</td>
<td>81</td>
<td>74</td>
</tr>
<tr>
<td>BDZ, %</td>
<td>51</td>
<td>58</td>
<td>33</td>
<td>53</td>
<td>66</td>
</tr>
<tr>
<td>Amphetamine, %</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Cannabis, %</td>
<td>19</td>
<td>39</td>
<td>9</td>
<td>65</td>
<td>62</td>
</tr>
<tr>
<td>Cocaine, %</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>15</td>
<td>14</td>
</tr>
</tbody>
</table>

Data are the percentage of positive results for each technique. The combined column combines the history and toxicology results to give a pattern of overall drug exposure for each infant. BDZ, benzodiazepine.
immature/atypical VEPs and fewer mature responses ($\chi^2 = 13.6, P = .001$) (Fig 3). All of these differences persisted after correcting for occipitofrontal head circumference, maternal smoking, and excess alcohol intake during pregnancy with a linear regression model for VEP amplitude and a binary logistic regression model for the prevalence of VEP components.

In utero methadone exposure in animal studies causes depletion of both acetylcholine and nerve growth factor in the brain as well as alterations in immature/atypical VEPs and fewer mature responses (Chi-squared = 13.6, P = .001) (Fig 3). All of these differences persisted after correcting for occipitofrontal head circumference, maternal smoking, and excess alcohol exposure in utero (Table 3).

VEP amplitudes, morphology, and implicit times did not differ among infants who showed no signs of NAS ($n = 24$), infants who developed mild NAS ($n = 28$), infants who developed moderate NAS ($n = 26$), or infants who required second-line therapy ($n = 22$).

Neonatal VEPs and In Utero Drug Exposure

Regression analysis confirmed that differences in VEP parameters persisted after correcting for other illicit drug use: VEP amplitude, $P = .012$; P1 response, odds ratio 0.02, 95% CI 0.00–0.16, $P = .001$; N2 response, odds ratio 0.27, 95% CI 0.09–0.84, $P = .024$. We found no associations between the prescribed maternal dose of methadone and amplitude, latency, or morphology of infant flash VEPs.

DISCUSSION

Substitute methadone is the currently recommended treatment of pregnant opioid-dependent women. Several observational studies have reported abnormalities of visual and neurologic development in infants of drug-misusing mothers prescribed substitute methadone in pregnancy but to date there has been no prospective study of such infants, and so the prevalence of visual dysfunction in this population remains unknown.

We have previously described abnormal flash VEPs in newborn infants exposed to methadone in utero but these data were confounded by IUGR and gestation, and numbers were too small to investigate the individual effects of methadone and other illicit drugs. This larger cohort study has confirmed substantial differences between neonatal flash VEPs of infants exposed to methadone in utero and those of non–drug-exposed comparison infants and suggests that prescribed substitute methadone, rather than other illicit drugs, may be to blame. Reduced VEP amplitude with immature waveform is consistent with the clinical finding of delayed visual maturation previously reported in similar but older populations.

In utero methadone exposure in animal studies causes depletion of both acetylcholine and nerve growth factor in the brain as well as alterations in...
dopamine, norepinephrine, and serotonin levels. Methadone has been shown to bind to ocular as well as to brain tissue in both adult humans and in animal models. Thus, a cause-effect relationship between in utero methadone exposure and abnormal infant VEPs is biologically credible, as well as consistent with a growing body of evidence linking maternal drug misuse with disordered infant visual development.

Strengths of this study were the large number of drug-exposed infants recruited (n = 100) and the detailed information regarding in utero drug exposure. Matching of comparison infants eliminated the potential confounding effects of gestation, birth weight, and socioeconomic group, and regression analysis allowed us to correct for other confounders, such as head circumference and maternal cigarette smoking and alcohol use. Nicotine has been shown to alter VEPs in animal models and so we used regression models to correct for the potential confounding effect of maternal cigarette smoking on neonatal VEP parameters. The high recruitment rate of 98% yielded essentially an unselected population of infants born to drug-misusing mothers. We found no relationship between early postnatal VEPs and the subsequent development of NAS, suggesting that the differences demonstrated in flash VEPs reflect in utero effects of maternal drug exposure, rather than the process of NAS itself.

Meconium analysis yielded a higher rate of positive results than most other techniques of drug exposure status; because the sensitivity of meconium analysis at detecting in utero drug exposure ranges from 77% to 95%, it is possible that even this detailed study underestimates the true extent of in utero drug exposure. Although we cannot rule out other contributing factors, such as poor maternal nutrition, our data strongly suggest that prescribed maternal substitute methadone, rather than associated illicit drug use, was the common factor associated with adverse in utero visuo-cortical development. The longer-term implications of abnormal neonatal VEPs in this cohort are not clear. Follow-up of this cohort is planned, to investigate whether these electrophysiological abnormalities manifest in later infancy as clinical visual problems, or resolve with time. In the meantime, it would be prudent to offer clinical visual follow-up to all infants born to drug misusing mothers prescribed methadone in pregnancy. Future studies should investigate alternatives to methadone treatment of pregnant opiate-dependent women. Because of reduced placental transfer, buprenorphine has theoretical advantages over methadone in the treatment of opiate addiction in pregnancy and limited published data suggest an advantage for infant neural development. Future studies must consider the confounding effects of alcohol, nicotine, and polydrug use, and include both short- and longer-term outcomes for the infant.

**CONCLUSIONS**

In utero exposure to prescribed methadone and other substances of misuse is associated with an alteration in visual electrophysiology in the newborn period suggestive of delayed visual maturation. These changes are associated with prescribed substitute methadone and do not appear to be specific to other drugs of misuse. The clinical significance of these alterations in neonatal flash VEPs is not yet clear and longer-term follow-up of this vulnerable cohort of infants is required to clarify the relationship between neonatal VEPs and subsequent visual and neuro-developmental outcomes. Any study of alternatives to substitute methadone in pregnancy must take account of effects on short- and longer-term cortical function in the infant.

**ACKNOWLEDGMENTS**

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**REFERENCES**


Neonatal Visual Evoked Potentials in Infants Born to Mothers Prescribed Methadone

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