

Effects of prenatal opiate exposure on brain development – a call for attention

Kristine B. Walhovd, Vibeke Moe, Kari Slinning, Torill Siqueland, Anders M. Fjell, Astrid Bjørnebekk and Lars Smith

The Perspective by Thompson, Levitt and Stanwood (Prenatal exposure to drugs: effects on brain development and implications for policy and education. *Nature Rev. Neurosci.* **10**, 303–312 (2009))¹ was very welcome. The authors' focus on the gap between scientific knowledge and societal policies is highly needed. In this regard, we find it timely to also point out the need to attend to potential effects of prenatal opiate exposure on brain development and their implications for policy and education, an issue not addressed by the authors.

Scientific documentation of opiate effects on fetal CNS development receives scarce attention relative to the special value it should have to societal policies and education: opiate problems predominate in the European drug treatment system². Next to alcohol, opiates are the most common substances abused by Americans admitted to treatment³, and the use of synthetic opiates, known as methadone maintenance therapy (MMT), is the recommended treatment in many nations for opioid-addicted pregnant women⁴. Hence, opiates are programmatically prescribed for thousands of developing brains. Two arguments are made for this: that MMT is a safe choice for these women and their children and/or that no good alternative exists. Both arguments might be true, but the two are sometimes confused, with the latter being taken to support the former. We believe that further knowledge about the effects of prenatal opiate exposure is valuable regardless of the principle argued, and find it remarkable that little literature exists describing possible teratogenic CNS effects of opiates in the developing child⁵.

Evidence from cell culture and animal studies raises concerns regarding possible adverse effects. Opioid receptors are present in several brain areas, and multiple mechanisms could be affected by opiate exposure⁶. Prenatal morphine exposure adversely

affects the migration and survival of neurons in rat embryos⁷. Morphine has also been found to increase apoptosis in human fetal microglia and neurons⁸, and recently prenatal heroin exposure in mice was shown to elicit memory deficits attributable to neuronal apoptosis⁹. Behavioural human studies are complicated by the potential effects of psychosocial and genetic factors and by the use of multiple drugs. Neonatal withdrawal effects are observed in the majority of opioid-exposed newborns¹⁰, and neuropsychological difficulties are documented in children that have been prenatally exposed to heroin^{11–13} and methadone¹⁴, but the latter vary with the type of comparison group employed¹⁵. Smaller neuroanatomical volumes and regionally thinner cortices compared to controls in children with heroin and poly-substance exposure are documented, partly linked to behavioural difficulties¹⁶. Such data are vulnerable to confounds, but they still yield important information. As recently reviewed⁵, non-invasive neuroimaging may shed light on the mechanisms of, serve as outcome predictors of, and improve the diagnosis of and the allocation of therapeutic resources to prenatal drug exposure. Unfortunately, no such data exist on cerebral characteristics in children exposed to MMT.

We strongly encourage increased attention to the potential effects of prenatal opiate exposure on brain development. Current data are scarce and partly complicated by interpretational problems. This should motivate further investigation of the effects of prenatal opiate exposure in the brain, so that health-care providers and policy makers can be sufficiently informed when making treatment programmes for pregnant opioid-dependent women and their children.

Kristine B. Walhovd, Anders M. Fjell and Astrid Bjørnebekk are at the University of Oslo, Institute of Psychology, Center for the Study of Human Cognition, POB 1094 Blindern, 0317 Oslo, Norway.

Vibeke Moe, Torill Siqueland and Lars Smith are at The Regional Centre for Child and Adolescent Mental Health East and South Norway, National Network for Infant Mental Health, Postboks 4623 Nydalen, 0405 Oslo, Norway and at the University of Oslo, Institute of Psychology, POB1094 Blindern, 0317 Oslo, Norway.

Kari Slinning is at The Regional Centre for Child and Adolescent Mental Health East and South Norway, National Network for Infant Mental Health, POB 4623 Nydalen, 0405 Oslo, Norway and at The Norwegian Institute of Public Health, Division of Mental Health, POB 4404 Nydalen, 0403 Oslo, Norway.

Correspondence to K.B.W.
e-mail: k.b.walhovd@psykologi.uio.no

1. Thompson, B. L., Levitt, P. & Stanwood, G. D. Prenatal exposure to drugs: effects on brain development and implications for policy and education. *Nature Rev. Neurosci.* **10**, 303–312 (2009).
2. European Monitoring Centre for Drugs and Drug Addiction. Technical data sheet — Monitoring the supply of heroin to Europe. EM/CDDA [online], http://www.emcdda.europa.eu/attachements.cfm/att_62086_EN_emcdda_tds_herointrafficking_2008.pdf (2008).
3. Substance Abuse and Mental Health Services Administration, Office of Applied Studies. Highlights for 2007 Treatment Episode Data Set (TEDS). Office of Applied Studies [online], <http://www.oas.samhsa.gov/TEDS2k7/highlights/toc.cfm> (2009).
4. National Institutes of Health. Effective medical treatment of opiate addiction. *NIH Consensus Statement* **15**, 1–38 (1997).
5. Derauf, C., Kakatpure, M., Neyzi, N., Lester, B. & Kosofsky, B. Neuroimaging of children following prenatal drug exposure. *Sem. Cell Dev. Biol.* (in the press).
6. Yanai, J. *et al.* Functional changes after prenatal opiate exposure related to opiate receptors' regulated alterations in cholinergic innervation. *Int. J. Neuropsychopharmacol.* **6**, 253–265 (2003).
7. Harlan, R. E. & Song, D. D. Prenatal morphine treatment and the development of the striatum. *Regul. Pept.* **54**, 117–118 (1994).
8. Hu, S., Sheng, W. S., Lokensgard, J. R. & Peterson, P. K. Morphine induces apoptosis of human microglia and neurons. *Neuropharmacology* **42**, 829–836 (2002).
9. Wang, Y. & Han, T. Z. Prenatal exposure to heroin in mice elicits memory deficits that can be attributed to neuronal apoptosis. *Neuroscience* 9 Mar 2009 (doi:10.1016/j.neuroscience.2009.02.058).
10. [No authors listed]. Neonatal drug withdrawal. American Academy of Pediatrics Committee on Drugs. *Pediatrics* **101**, 1079–1088 (1998).
11. Suess, P. E., Newlin, D. B. & Porges, S. W. Motivation, sustained attention, and autonomic regulation in school-age boys exposed *in utero* to opiates and alcohol. *Exp. Clin. Psychopharmacol.* **5**, 375–387 (1997).
12. Slinning, K. Foster placed children prenatally exposed to poly-substances—attention-related problems at ages 2 and 4 1/2. *Eur. Child Adolesc. Psychiatry* **13**, 19–27 (2004).
13. Moe, V. Foster-placed and adopted children exposed *in utero* to opiates and other substances: prediction and outcome at four and a half years. *J. Dev. Behav. Pediatr.* **23**, 330–339 (2002).
14. Hunt, R. W., Tzioumi, D., Collins, E. & Jeffery, H. E. Adverse neurodevelopmental outcome of infants exposed to opiate *in-utero*. *Early Hum. Dev.* **84**, 29–35 (2008).
15. Jones, H. E., Kaltenebach, K. & O'Grady, K. E. The complexity of examining developmental outcomes of children prenatally exposed to opiates. A response to the Hunt. *et al.* Adverse neurodevelopmental outcome of infants exposed to opiates *in-utero*. *Early Human Development* (2008, **84**, 29–35). *Early Hum. Dev.* **85**, 271–272 (2009).
16. Walhovd, K. B. *et al.* Volumetric cerebral characteristics of children exposed to opiates and other substances *in utero*. *Neuroimage* **36**, 1331–1344 (2007).