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

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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 system[2]. Next to alcohol, opiates are the most common substances abused by Americans admitted to treatment[3], and the use of synthetic opiates, known as methadone maintenance therapy (MMT), is the recommended treatment in many nations for opioid-addicted pregnant women[4]. 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 child[5].

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 exposure[6]. Prenatal morphine exposure adversely affects the migration and survival of neurons in rat embryos[7]. Morphine has also been found to increase apoptosis in human fetal microglia and neurons[8], and recently prenatal heroin exposure in mice was shown to elicit memory deficits attributable to neuronal apoptosis[9]. 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 newborns[10], and neuropsychological difficulties are documented in children that have been prenatally exposed to heroin[11–13] and methadone[14], but the latter vary with the type of comparison group employed[15]. Smaller neuroanatomical volumes and regionally thinner cortices compared to controls in children with heroin and poly-substance exposure are documented, partly linked to behavioural difficulties[16]. Such data are vulnerable to confounds, but they still yield important information. As recently reviewed[5], 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.

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