Commentary on Gibson et al. (2017): Gestational age and the severity of neonatal abstinence syndrome

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"*Neonatal abstinence is difficult to assess in preterm infants, and the pros and cons of opioid replacement treatment are not clear. Clinicians should be aware of potential longer term issues for in-utero opioid-exposed children, regardless of neonatal manifestations.*"

Gibson et al.'s retrospective study highlights an important issue, and adds to the debate around whether preterm infants are as likely as their term-born compatriots to develop significant neonatal abstinence syndrome (NAS) following in-utero opioid exposure [1-3]. In a large cohort (n = 102) of late preterm infants (gestational ages 34–36 weeks), the likelihood of receiving pharmacological treatment for NAS was not different compared to babies born at later gestations. These data are of particular interest in light of recent rises not only in the number of illicit opioid using mothers, but also in mothers on prescribed opioids, and indicate that concerns regarding the development of NAS following maternal opioid use in pregnancy should not influence timing of delivery [4, 5].

Although initiation of opioid replacement therapy was not influenced by gestation, median duration of treatment for late preterm infants was significantly shorter (by approximately 30%) compared to infants born at term. The authors postulate that this may be due to differences in placental opioid transport related either to gestation or concomitant illicit drug use, reduced cumulative opioid exposure, slower postnatal opioid excretion, neurological immaturity or a combination of factors [1, 6]. In common with many other workers, Gibson et al. described use of a modified Finnegan score to assess the severity of NAS, but carers should be aware that no scoring system is well validated in the preterm population. A recent study compared preterm babies born at gestations ranging from 33 to 36 weeks with babies born at term, and noted gestation-related changes in a variety of Finnegan scoring criteria, some of which (e.g. tachypnoea) would increase, and some of which (including sleep disturbance and sweating) would decrease the cumulative Finnegan score [7]. NAS is ameliorated by rooming-in as well as by breast feeding [8]; in Gibson's study late preterm infants were more likely to be admitted to the neonatal unit, which may have occasioned closer observation and documentation of milder signs of NAS. None of the mothers of the late preterm infants was homeless, which may have been associated with a less unstable life-style and less illicit drug use, but numbers were small. There was no significant interaction between maternal maintenance treatment, gestational age and the likelihood of the baby receiving treatment for NAS, but only a small proportion of mothers in Gibson's study had been maintained on buprenorphine, and so there may be a type II error. Less severe NAS has been described by others for babies born to buprenorphine, compared to methadone-maintained mothers [9, 10].

Opioid withdrawal in the newborn is a complex and incompletely understood process with considerable longer-term effects. Increasing evidence points to adverse effects of opioid exposure upon the developing brain, with disproportionately small head circumference at birth and abnormal cortical visual evoked potentials [11-13]. Preliminary magnetic resonance imaging (MRI) data indicate reduced brain volume in term opioid-exposed babies [14]. In an Australian cohort of 230 very preterm infants, cortical volumes tended to be smaller at term in those who had received morphine analgesia, and this was associated with behavioural dysregulation persisting to age 2 years [15]. While there are currently no data to indicate adverse effects of morphine used postnatally to treat opioid withdrawal in the newborn period, such treatment should not be considered proven safe. Practice varies widely; Gibson et al. report a median treatment duration of just over 3 weeks, whereas others have described a median treatment period of 10 days for similarly exposed term infants [2]. Abnormalities of cortical visual function persist at least to 6 months of age in term babies born to methadone-maintained mothers and up to 40% of these babies fail clinical visual assessment, with a very high incidence of nystagmus [16]. Interestingly, abnormalities of visual function in the first year of life do not seem to be related to manifestation of NAS, raising issues concerning arrangements for follow-up of these vulnerable children [13, 16].

Opioid-dependent pregnancies are more likely to result in preterm birth, but we currently lack a well-validated assessment tool for NAS in this population. All babies born to opioid-dependent mothers should be considered at risk of longer-term visual, behavioural and neurodevelopmental problems and should be followed-up, regardless of manifestations of NAS in the newborn period.

References

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