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REVIEW ARTICLE

Consequences of prenatal opioid use for newborns

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ABSTRACT

One-third of childbearing women take prescription opioids, previously occurring only in 6–7% of pregnant women. Prenatal opioid exposures may cause birth defects, altered brain development and neonatal abstinence syndrome (NAS). NAS incidence increased fourfold and length of stay increased from 13 to 19 days over 10 years (2004–2013), leading to sevenfold increases in NICU days due to NAS. Initial data suggest that recent NAS increases have resulted from increased use of prescription opioids rather than illicit drugs.

Conclusion: Paediatricians will have to manage the consequences of prenatal opioid exposures, as the offspring often have complex medical and social issues associated with these families.

Neonatal abstinence syndrome (NAS) has become one of the fastest growing reasons for neonatal hospital admissions in the United States (1). Opioid use during pregnancy increased from 1.2 to 5.6 per 1000 hospital births per year and NAS incidence increased from 1.2 to 3.4 per 1000 hospital births per year between 2000 and 2009 (2). Tolia et al. (1) reported that NICU admissions for infants with NAS increased from 7 to 27 cases per 1000 admissions, with greater increases in 2009–2013 than in 2004–2008. Median lengths of stay also increased from 13 to 19 days as more infants received pharmacotherapy (74–87%); thus total NICU days attributed to NAS increased sevenfold from 0.6% in 2004 to 4.0% in 2013 (1). On average, one infant with NAS is hospitalised every hour in the United States with parallel increases worldwide (3).

Abbreviations
CDC, Centers for Disease Control and Prevention; HIV, Human Immunodeficiency Virus; NAS, Neonatal Abstinence Syndrome; NICU, Neonatal Intensive Care Unit; U.S., United States of America.

The reasons for this epidemic are unclear, but most evidence points to prescription opioids, not illicit drugs such as heroin. In Tennessee, for example, 63% of NAS cases occurred in women receiving prescription opioids, whereas only 33% occurred among women using illicit or diverted substances (4). Further, morphine use increased from 49% in 2004 to 72% in 2013, and methadone use actually decreased (1) Previous studies had found only 6–7% of pregnant women using opioids (5), but the Centers

Key notes

- The use of prescription opioids has increased markedly among women of childbearing age groups, which may lead to birth defects, altered brain development and neonatal abstinence syndrome (NAS).
- NICU days for NAS admissions have increased sevenfold over the past 10 years (2004–2013).
- Paediatricians should learn to manage the consequences of prenatal opioid exposures, dealing with complex medical and social issues in these families.

for Disease Control & Prevention (CDC) recently reported one-third of U.S. women aged 15–44 years taking prescription opioids (6). Among them, 39% on public insurance and 28% on private insurance had filled opioid prescriptions; this was 1.5 times more likely among White women than among African American or Hispanic women (6). Using Medicaid data from 46 U.S. states, Desai et al. (7) found an absolute risk of NAS in 5.9 per 1000 deliveries from prescription opioids in pregnant women, further accentuated by long-term use [relative risk (RR) 2.05 (95% confidence intervals (CI) 1.81–2.33)] and opioid use in late pregnancy [RR 1.24 (95% CI 1.12–1.39)] (7). CDC Director Dr. Tom Frieden commented 'Taking opioid medications early in pregnancy can cause birth defects and serious problems for the infant and the mother' (8). Major risks from prenatal opioid exposure not only include birth defects (early pregnancy), but also altered brain development (throughout pregnancy) and NAS (late pregnancy).

However, the long-term consequences of illicit drugs or opioid maintenance therapy cannot be underestimated. After adjusting for confounders, illicit opioid abuse was associated with increased odds of preterm labour, early onset delivery, poor foetal growth, prematurity and stillbirth (9). Such effects are less likely among pregnant women receiving appropriate analgesia for surgery or painful procedures. Another study found increased odds of maternal death (4.6-fold), cardiac arrest (3.6-fold), intrauterine growth restriction (2.7-fold), placental abruption (2.4-fold), preterm labour (2.1-fold), oligohydramnios (1.7-fold), stillbirth (1.5-fold) and premature rupture of membranes (1.4-fold) associated with illicit opioid abuse (10). Preterm birth occurred three times more commonly in primiparous mothers hospitalised for opioid abuse (±other drugs), and their babies were six times more likely to require NICU admission (11). It is evident, however, that improved neonatal outcomes result from structured treatment programs (12).

Compared to alcohol, prenatal opioids may not consistently cause birth defects in humans. Animal studies suggest an association of prenatal opioids with increased incidence of neural tube defects (13,14). One large, multicenter study suggested that conoventricular septal defects (OR, 2.7), atrioventricular septal defects (OR, 2.0), hypoplastic left heart syndrome (OR, 2.4), spina bifida (OR, 2.0) or gastroschisis (OR, 1.8) in infants may be associated with maternal intake of opioids other than buprenorphine (15). A population-based study from Finland found birth defects in 10% of children from mothers receiving buprenorphine in pregnancy illicitly or as medical treatment for opioid dependence; mostly involving congenital heart disease, urinary collecting system defects, ophthalmic and maxillofacial defects (16). Although this area is evolving, other studies do not support increased risks of structural congenital malformations following prenatal opioids (17,18).

Prenatal opioid exposure does change the timing and quality of myelination by disrupting oligodendrocyte development (19), decreases dendritic growth (20) and branching patterns (21) of pyramidal neurons in the cortex and suppresses cell proliferation and neuronal migration to the cortical plate (21). These effects may reduce regional brain volumes in the basal ganglia (22) and other brain areas (23), with long-term changes in subsequent behaviour (24–26), autonomic regulation (24), visual-motor (27), strabismus (28), or swallowing (29) dysfunctions and lower developmental potential (30–32). Current data cannot clearly differentiate between the long-term neonatal outcomes resulting from the prenatal use of prescription opioids, illicit drugs or opioid maintenance therapy.

Buprenorphine and methadone form the mainstay of opioid maintenance therapy during pregnancy. Buprenorphine is considered an attractive alternative, partly due to more favourable neonatal brain growth patterns (33); however, its long-term use cannot be considered benign and has been associated with poor child outcomes to three years of age (16). Regular follow-up during pregnancy and breastfeeding may enhance brain growth and encourage these women to abstain from using tobacco, alcohol or illegal drugs (34); factors associated with higher likelihood of NAS (7); as well as decreasing the severity of NAS in their infants (35,36). It is heartening to note that the proportion of infants with NAS receiving breastmilk increased from 20% in 2004–2005 to 35% in 2012–2013 (1).

The NAS epidemic is perhaps the most prominent consequence of prenatal opioids, with limited evidence for its management (37–41). Lack of evidence-based guidelines for weaning neonatal opioids or treating NAS contributes to prolonged hospitalisations and hospital readmissions for NAS infants, both of which are extremely expensive (42,43). Estimated costs for infants requiring treatment for NAS range from $49 000 to $58 000 with hospital stays averaging 12–16 days (2,44,45). For example, Ohio reported over $70 million in charges and nearly 19 000 hospital days in 2011 resulting from NAS (46). The medical and social management of these infants is complicated by prenatal exposures to multiple drugs, maternal incarceration, complex and/or violent family situations, nutritional deficiencies, transmission of HIV or other infections (47). It is a travesty that these neonates are frequently excluded from studies of neurodevelopment, neuroimaging (48), or pain management (49,50), thereby contributing to the paucity of evidence available for their management.

Many questions remain unanswered on how to manage neonatal drug withdrawal or treat the procedural, surgical or prolonged pain occurring in neonates with NAS. Many newborns are exposed to repetitive or continuous pain because of their prolonged hospitalisations and associated comorbidities, which accentuates their suffering from NAS. Drug abusing mothers are often abandoned by their families, criminalised by society and burdened with a social stigma. The mother–infant dyads often face an unstable social environment. Some social and healthcare workers may treat them with contempt and may be unwilling to offer the most effective NAS treatments to their infants in the hospital or in the clinic. These barriers to improving their medical care contribute to poor knowledge uptake and

practice changes by healthcare providers, nursing and family members (51,52).

For these babies and their families, much additional work is needed to help diminish their immediate suffering and to better understand the ways to optimise their short-term and long-term outcomes. Reducing opioid use and misuse during pregnancy is, however, the first step for preventing these complications in newborns and children.

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CONFLICT OF INTEREST

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