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After NAS

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ABSTRACT

Mothers have used opioids for thousands of years but neonatal abstinence syndrome (NAS) or rather, survivors of NAS, is a modern phenomenon. Unrecognized and/or untreated opioid withdrawal was almost always fatal but with greater awareness and standardization of treatment, NAS is now an uncommon direct cause of infant death. However, opioids are now increasingly accessible and potent and the outcomes of children after the neonatal period are of great concern, especially when coupled with multiple other social and health risks. Complex individual, environmental and genetic factors need to be considered when assessing outcomes or future research for babies with NAS. Any intervention or research efforts must address these multifactorial complexities. This review will discuss pertinent post neonatal outcomes, including mortality, physical and mental health and social functioning of children with a history of NAS.

Practice points

- The problems caused by maternal drug use does not stop during the neonatal period. Children with known prenatal drug exposure, especially those diagnosed with NAS, need long-term multidisciplinary support.
- Any support must also involve the family and take into consideration the intergenerational effects of maternal substance use
- Simple interventions and diagnostic procedures e.g. sleep studies, maternal education, may substantially decrease the risk of death and/or poor outcomes for affected children

Research directions

- The role of early childhood and family intervention to decrease risk of neurodevelopmental, social and other health repercussion of intra-uterine opioid exposure
- Determining the relationship between severity of NAS and neuroanatomical changes to future cognitive and academic function
- Epigenetic influence on long-term resilience and adversities after known intra-uterine opioid exposure.

1. Introduction

Until this century, the long-term outcomes of infants of opioid-using mothers were not well known. Most infants died soon after birth. “Congenital Morphinism”, as neonatal opioid withdrawal was known because morphine was the most commonly used opioid, was first described in Western literature in 1875 [1]. Then, outcomes were dismal. In one report, 15 of 16 infants from one mother died. The sole survivor was given a few drops of morphine which led to rapid resolution of symptoms that included poor feeding, diarrhea, failure to thrive, seizures. If untreated and unrecognized, these problems usually led to death, often within a few days to weeks of birth [2].

In the 1970's, the term “Neonatal Abstinence Syndrome” (NAS) was used to describe the withdrawal syndrome experienced by babies of narcotic-using mothers [3]. The 21-point assessment tool, known as the Finnegan Scoring System, allowed for the standardization of diagnosis, assessment and treatment of narcotic-exposed infants. This led to increasing awareness and the need for treatment of withdrawing infants. Today, NAS is an uncommon direct cause of infant death, most babies with NAS will survive and leave their birth hospital in a healthy condition, including those requiring extra support with neonatal intensive care [4].

The longer-term outcomes of children after NAS are therefore a relatively new concern. In the last few decades, the numbers of mothers using opioids, and consequently, the numbers of babies with NAS, have increased exponentially around the world [5]. Each year, thousands (if not millions) of babies are born to opioid-users. Although vast resources are spent on ensuring healthy results within the hospital [6], little is

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known about their future trajectory. This is of great concern because NAS is the result of maternal drug use which in turn, is often intimately and inextricably intertwined with multiple and complex environmental, social and genetic factors that have the potential to compound the direct effects of maternal drugs. These problems, unlike NAS, may not resolve with time and taken together, may compound the risk of undesirable and considerable individual, intergenerational and societal harm for the child with NAS.

2. How opioids have changed over the years

Opioids have been used by humanity for thousands of years. The earliest reference to the cultivation and use of opium came from lower Mesopotamia, in Southwest Asia, where the poppy plant was known as the *Hul Gil* ("joy plant") by the Ancient Sumerians. Throughout history, opium derivatives have been used extensively in religious ceremonies and rituals around the world by all cultures. The Ancient Greeks and Romans used opium for its analgesic, hypnotic and constipating properties. Seventh century records showed that the Chinese of the Tang and later, the Song Dynasties, used opium for a myriad of conditions, including diarrhea, male infertility and congestive cardiac failure [7].

In 1803, morphine, the principal active ingredient of opium, was isolated by the German scientist, Friedrich Sertürner. Morphine is 10,000 times stronger than opium and was named by Sertürner for the Greek god of sleep, Morpheus. Morphine was quickly shown to be an extraordinarily effective analgesic, even in the worst of conditions but it was also found to be very addictive. In the American Civil War, more than half a million soldiers became morphine-addicts after being treated with morphine for battle injuries [8].

Regardless, the importance of opioids, and in particular, morphine, as a therapeutic agent was undeniable. In the 19th century, a well-meaning but unfortunately, misdirected roller-coaster quest for a less addictive but not less effective type of opioid ensued. This led to the development of diacetylmorphine, or heroin in 1874 by Charles Alder Wright, an English chemist who manufactured heroin by boiling morphine with acetic anhydride, a commonly available colourless liquid that is used for various industrial processes, including the manufacture of cellulose acetate (photo paper) and aspirin [9]. Heroin was considered much safer and less addictive than morphine and was aggressively marketed by the pharmaceutical company, Bayer, as a safe panacea for morphine addiction. It was dispensed liberally as a cough suppressant for children and could be obtained without prescription. In reality, heroin was up to 4 times more potent than morphine on a weight for weight basis [10] and its addictive qualities were soon apparent, leading to the passing of laws such as the Heroin Act (USA 1924) [7]. This rapidly drove heroin trade into the illegal and underground market.

Since then, increasingly potent and addictive forms opioids have been developed. Fentanyl, for example, is a lipophilic and rapidly acting opioid analogue that was first made by chemist Paul Janssen in 1959. Fentanyl is several thousand times more potent than morphine [11], is relatively cheap and can be administered in a multitude of ways, e.g. intravenously, transdermally, nasally or orally. In 2016, fentanyl was linked to > 20,000, or > 50% of all opioid-related deaths in the USA. Of note, fentanyl, including many of the most commonly abused opioids (e.g. codeine, pethidine) can now be legally obtained by medical prescription. Indeed, legal opioids are responsible for more opioid-related deaths than heroin and cocaine combined [12].

3. Women, children and opioids

In contrast to alcohol, opium, and later, morphine, were considered acceptable for female use. Morphine was liberally prescribed for "women troubles" [7] and indeed, many morphine addicts were created after they were prescribed morphine for child-birth related pain. Even the wife of the inventor of the hypodermic syringe, Alexander Wood, Rebecca Massey, was rumoured to be the first intravenous morphine addict [7]. Opioids were viewed for centuries as a benign medication that could be liberally consumed not only by women, but also by their children. Evidence from around the 16th Century BC suggested that poppy plant mixtures (e.g. with wasp droppings) were used by the Ancient Egyptians to calm crying infants. Opium was known as the poor child's nurse in the 19th Century [7], where it administered extensively to keep children quiet in asylums, orphanages or in poorer communities where parents had to work [7]. This practice was widespread even despite the well-known dangers of narcotization and child death. Many children died from inadvertent or chronic intoxication due to inconsistencies in dosage and medication strength [13]. Thousands, if not millions, of children over thousands of years, have therefore been exposed to opioids, either via their mother or from postnatal sources. Opioids, however, are now more potent than ever and combined with increasing ease of availability, particularly of legal opioids, is reflected in an exponential increase in the number of newborn infants diagnosed with NAS [5].

4. Why worry after NAS?

Even though most infants with NAS are healthy and will survive the acute consequences of withdrawal if they are appropriately treated [14], NAS implies prenatal opioid exposure during critical periods of fetal development. Opioids are neuroteratogens that impair neuronal development and function. Opioids accelerate neuronal apoptosis [15] and even a few days of morphine exposure in healthy adults leads to rapid cognitive dysfunction [16]. The effects of prenatal opioid-exposure in children on neurodevelopment are unclear but opioid-exposed infants consistently have smaller head sizes and on MRI, have lower brain volumes [17], a finding correlated strongly with intelligence levels within the general population [18].

Opioid-exposed families may also have lifestyle, psychological and genetic issues that have the potential to compound direct drug effects. Welfare and social issues such as lifestyle stress, poverty, malnutrition and poor parental education are synergistic negative influences on childhood neurodevelopment and function [19]. Drug-exposure may lead to epigenetic changes that in turn, have the potential to transmit addictive and other negative behaviors throughout generations [20]. Unfortunately, these very factors exacerbate the difficulties in determining outcomes after NAS because children, more often than not, are lost to long-term follow-up and intervention. Furthermore, whether differentiation can be made between children who are opioid-exposed but not withdrawing enough to be diagnosed with "NAS" (i.e. ICD 10 code P96.1) [21] is also unclear. Nevertheless, there are specific issues that need to be addressed in the context of exposure to maternal use of addictive drugs and these will be discussed separately in the following sections of the review.

5. Specific issues

5.1. Are children with NAS more likely to die?

If promptly recognized and adequately treated, NAS and therefore intra-uterine opioid-exposure, is an uncommon direct cause of infant death [2]. Indeed, intra-uterine drug-exposure may even be associated with better early life survival. In a population-based study of infants admitted to neonatal intensive care units (NICU) in Australia, Abdel-Latif et al. found a significantly lower mortality rate in 310 infants of heroin/methadone-using mothers when compared to other infants, despite a higher incidence of adverse factors such as out-born birth, antepartum hemorrhage, chorioamnionitis and lower steroid prophylaxis (adjusted OR 0.51, 95% CI: 0.28–0.96) [4]. Although the exact etiology of this association is uncertain, opioids or stress may accelerate pulmonary maturation and hence, improve early survival. Heroin-exposed preterm infants are noted to have less severe respiratory distress

than other infants [22]. Pups of rabbits injected with heroin have improved lung maturation and compliance that are equivalent to 3 days increase in gestation [23]. Stress from repeated episodes of drug withdrawal is also associated with increased placental corticotrophin-releasing hormone (CRH), maternal cortisol levels and accelerated lung maturity [24].

However, after the neonatal period, children with a history of NAS or opioid-exposure are more likely to die than other children. Evidence from epidemiological studies suggest that this risk persists until adolescence and is secondary to external factors such as maltreatment, accidents and trauma, regardless of the cultural background [25,26]. In an analysis of linked administrative data, Uebel et al. showed that mortality rates for 3,842 Australian children with a diagnosis of NAS were three-fold higher than 1,018,421 children without NAS (OR 3.3, 95% CI 2.4–4.4). Children with NAS were most likely to die between 28 days and 1 year of age (OR 7.6, 95% CI 5.3–11.0), coinciding with discharge from the hospital of birth. The most common causes of death were from Sudden Infant Death Syndrome (SIDS, OR 10.7, 95% CI: 5.3–21.8), accidents (OR 7.4, 95% CI 2.7–19.9) and assaults (OR 39.8, 95% CI 11.8–134.0). Deaths were also more likely to occur without prior hospital admissions (suggesting that the child was previously healthy) and to be referred for further examination (e.g. autopsy), suggesting that the death was unexpected or unexplained by health reasons [25]. Similar outcomes were also noted in opioid-exposed Taiwanese children without a specific diagnosis of NAS. Of 3210 children born between 2004 and 2009 to parents with opioid use disorders (25% on methadone treatment programs), those of opioid-using parents were more likely to die from “unnatural” e.g. injuries and accidents than non-exposed children (standardized mortality ratio, SMR: 4.23, 95% CI: 2.37–6.97), with low birth weight and paternal opioid dependency increasing risks by 2.5–5.2 fold [26].

Whether there are inherent risks within opioid-exposed children to increase their risk of mortality are unclear and needs further study. Death from Sudden Infant Death Syndrome (SIDS) may be up to 10-times higher in infants of substance-using mothers [27] as well as fathers [28] than in the general population. The exact cause of this is unclear and may be due to a combination of physiological differences as well as environmental factors (e.g. safe sleeping techniques, parenting behavior, etc). Intra-uterine opioid-exposure is associated with an exaggerated decrease in minute volume in response to hypoxia and hypercarbia [29], which may result in an ability of the infant to generate an appropriate ventilatory response during stress (e.g. smothering in bed clothes). Opioids may also impair sleeping patterns creating longer sleep times, greater apnoea durations, more periodic breathing [30], and more REM, resulting in less quiet and more disorganized sleep [31]. In animal studies, intra-uterine morphine and withdrawal causes a state of arousal, with loss of REM sleep and increased risk of preterm birth and fetal death [32]. Such abnormalities may resolve with resolution of withdrawal [33] but may indicate central nervous system immaturity. Regardless, short-term sleep deprivation and REM-sleep associated obstructive apnoea increases the risk of SIDS [34] and whether polysomnography has the potential of reducing this risk in opioid-exposed infants is unknown and deserves further consideration.

5.2. Are children with NAS at risk of poor physical health?

Information about physical health outcomes after NAS are again, unfortunately, nebulous because of the scarcity of long-term data. In a follow-up of 192 opioid-exposed children, three, who were treated for opioid withdrawal, were “sickly” (n = 1), blind (n = 1) and deaf (n = 1) [14]. In an Australian cohort of 3,842 children with NAS, Uebel et al. found that NAS was independently associated with a higher rate of hospitalization until adolescence but the most common reasons for hospitalization were due to external factors such as maltreatment, poisoning and assaults rather than illnesses inherent to the child [35]. Nevertheless, as many as 25% of opioid-exposed children may not receive necessary health-care within the first 2 years of life [36], compounding the need for hospitalization of common childhood problems, including infections [37]. Providing easily accessible, peer based and advocacy programs that allows for non-punitive, non-judgmental and cheap health care access for opioid exposed families may decrease the need for hospitalization, especially during early childhood [38].

5.3. Mental health disorders (MHD)

MHDs are intertwined with drug abuse. People with MHD are more likely to use drugs and vice versa. In a longitudinal examination of 2,000,118 patient records from the Taiwan National health Insurance Research Database between 2000 and 2009, 124,423 people with selected mental health disorders including affective psychoses, neurotic disorders, schizophrenia, personality disorders and adjustment reactions, were up to 5 times (Hazard Radio 5.09, 95% confidence interval: 4.74–5.48) more likely to develop substance use disorders. The risk increased to 14.55 times if patients were aged between 10 and 19 years [39]. Parental drug-use, per se, also increases the risk of MHD, including anxiety and affective disorders in children [40] and in young adulthood [41]. However, the risk may be modified by genetic and environmental influences. Offspring of drug-users, for example, are at increased risk of ADHD but this risk is mitigated by adoption [42]. A study of 94 opioid-exposed children found an increased risk of ADHD with maternal but not paternal opioid use even though all parents had a higher carriage risk of risk alleles for ADHD [43].

Unfortunately, maternal use of opioids and other drugs is intimately associated with multiple risk factors for poor childhood mental health outcomes. In a linked study of 65,117 children born in Finland in 1991, Jääskeläinen et al. noted an increased risk of MHD by 5.5-fold if a child had multiple parental risk factors including maternal substance use, mental disorders non-intact family and social welfare need. Girls were at higher risk than boys and risk was only ameliorated slightly by improved maternal education [58]. Linked data analysis by Uebel et al. of an Australian cohort demonstrated more specifically that children with a history of NAS were significantly more likely to be hospitalized for “mental and behavioral disorders” including mental retardation (OR 2.8), psychological disorders (OR 2.9), including speech and language disorders (OR 3.6), autism (OR 3.6) and behavioral and emotional disorders (OR 4.1) [46].

The etiology of increased risk of MHD is unclear but any childhood stress could lead to disruption of developing cortical structures, particularly in areas of the brain governing social behavior and anxiety, such as the parahippocampal gyri and middle temporal gyrus, respectively [44]. In children exposed specifically to maternal opioids, MRI scans indicate altered maturation of connective tracts, which may be associated with cognitive and behavioral difficulties [45]. Certainly, future intervention and research efforts should incorporate long-term assessment and support for risk of MHD development.

5.4. Addiction and other adverse social outcomes

Addiction is a form of MHD and prenatal substance exposure predicts future drug use drug use by up to 50% [46]. This is not new information. Of the 192 opioid-exposed infants reviewed by Cobrinik et al., in 1959, three patients who had been treated for withdrawal as newborn infants, became “addicts” at age 10, 12 and 58 years [46]. The neuropathology associated with an increased risk of drug-seeking behaviors is unclear, but lower basal ganglia volumes [17] is also noted in patients with poor impulse control and addictive behaviors [47], possibly due to lower levels of dopamine and other neurotransmitters [48].

Environmental modification of drug-seeking behaviors, however, are vital. Three inter-connecting traits are common to families affected by drug-use: parenting behavior, environmental deprivation and peer influence [49]. Almost half (45%) of child laborers aged 5–15 years in Surat City, India used drugs including tobacco, snuff, alcohol, cannabis

and opium but this was done mainly to negate the negative aspects of daily life [50]. Drug-using parents are less adaptive and responsive owards the needs of their children [51] and this, along with environmental deprivation and stress, could lead to early life physical and mental health issues including social disorientation and adverse behaviors such as drug use.

Deviant behaviors may start young but may not be noticed until later life. In an interview of 285 predominantly African-American children of addict mothers aged 12–17 years, 64% had committed a deviant act (e.g. fighting, disobeying parents and police officers, shoplifting, trespassing, damaging property, stealing, carrying a deadly weapon, dealing in stolen goods) by 11 years of age (mean 8.3 (2.2) years), 21% had used illicit drugs (mostly marijuana) (mean 13.1 (1.5) years) and 37% had used alcohol (mean 12.3 (2.6 years), with 16% reporting drinking to intoxicated states. Negative behaviors were compounded by a lack of family structure and positive home atmosphere. Only 39% had an intact family (continuous presence of both birth parents) and only 18% reported a positive and encouraging home environment [52].

Indeed, psychological issues, usually of hostility, depression and impulsivity is common [53] and consistently predicts early drug-use. This suggests that multi-focused programs with a trauma-focused approach are needed to best address the continuum of emotional needs of children of drug-users. Certainly, any intervention needs to take in the whole family and not the child because parental modelling is crucial in the lead-up to future addiction and other divisive behaviors.

5.5. Neurocognitive function and school performance

Opioid-exposure is associated with poor neurodevelopment. The exact impact of opioids on neurogenesis and function is unclear but opioids induce apoptosis of human brain cell cultures in vitro [15], impair synaptosomal uptake of neurotransmitters like dopamine and norepinephrine [54] and impair cognitive function, even after a few days of exposure [16]. Children exposed to prenatal opioids have smaller head circumferences that persist until adolescence [55] but there is no firm relationship between neuroanatomical changes and cognitive testing. In 23 children exposed to opioids and multiple substances, neither brain volume or cortical thickness correlated to cognitive outcomes [56].

In a meta-analysis of 26 studies comprising 1,455 children exposed to prenatal opioids and 2,982 controls, Yeoh et al. found that prenatal opioid exposure was significantly associated with poorer mental and physical development from as early as 6 months. Cognitive differences persisted until adolescence with standardized mean differences (95% Confidence Intervals) in test scores varying between 0.52 (0.31–0.74) at age 0–2 years, 0.38 (0.07–0.69) at ages 2–6 years and 0.44 (−0.28–1.16) at ages 6–18 years (not significant at this age). Motor score differences were 0.49 (0.23–0.74) lower in opioid-exposed children between 2 and 6 years [57].

The relationship between cognitive tests in early childhood and future academic performance is not certain - there is no data relating neurodevelopmental testing with school outcomes. Oei et al. used linked analysis to determine performance in Australian curriculum-based tests until the first year of high school (ages 12–13) for 2,234 children with a previous diagnosis of NAS. Compared to socio-economically matched controls (n = 4,330) and to other children (n = 598,265), children with NAS scored significantly lower in standardized testing than other children from as early as grade 3 (ages 8–9 years). By grade 7, their scores were lower than other children in grade 5 (average 2 years younger). The risk of not meeting minimum standards was independently associated with NAS (adjusted odds ratio, 95% confidence interval, 2.5, 2.2–2.7), indigenous status (2.2, 2.2–2.3), male gender (1.3, 1.3–1.4), and low parental education (1.5, 1.1–1.6) [58].

Unfortunately, the association between school failure and poor adult outcomes is undisputed and strong. Children who fail at school or who do not read at grade level, even from as early as ages 8–9 (grade 3) are more likely to use drugs, engage in criminal activity, be incarcerated, be unemployed and earn less [59]. These results suggest that children with a known history of NAS, especially if they have other risk factors such as having younger Indigenous mothers, male gender, being a rural resident, should be targeted for specific neurodevelopmental intervention in a similar manner to children with other risk factors e.g. prematurity. Such intervention has been shown to be cost effective and have effects that transcend generations, even in the highest risk communities. Intervention, however, must include the family. The ABCDERIAN project randomized 111 high risk (98% African American) infants to an intervention problem of early childhood education. At age 30, 101 of the original subjects demonstrated significant benefits, including higher years of education [60]. Other early childhood education programs have consistently shown benefits in other areas, including lower rates of juvenile and violent arrests, school drop outs, and need for special education services, especially in boys.[86] In addition, the cost-effectiveness of these programs cannot be denied. A review of programs focusing on 3–4 year old high risk children found a return for up to $10 USD for every dollar spent on the programs, with benefits lasting up to the 3rd decade of life [61].

5.6. Adulthood

Currently, there is little data linking NAS to adult outcomes. Herranz et al. conducted a series of interviews with 30 heroin-exposed adults (mean age 22.3 years) with a postnatal diagnosis of NAS in Spain. Adverse problems in this cohort was evident from early childhood. Of the original cohort of 151 children, five had died (four from AIDS, one of unknown reasons), 94 were not contactable. Up to 40% of their mothers and 30% of fathers had died, 23% were adopted/fostered before childhood and emotional and physical abuse were reported by 25%. One in 5 were diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), 87% had used cannabis and 47% had used cocaine. Half were educated beyond school but 37% were unemployed, 57% had received psychiatric treatment during childhood [62].

6. The future

Article 33 of the United Nations Convention of the Rights of the Child, specifically states that “States Parties shall take all appropriate measures, including legislative, administrative, social and educational measures, to protect children from the illicit use of narcotic drugs and psychotropic substances as defined in the relevant international treaties, and to prevent the use of children in the illicit production and trafficking of such substances.” [63] Even though extraordinary resources are spent on ensuring prompt, timely and safe treatment of infants with or at risk of NAS, very little is known of their outcomes. Available data show that a combination of adverse factors, including direct drug effects, genetic influences and environmental issues have the potential to lead to extremely poor outcomes for most opioid-exposed children including future drug use. NAS is like prematurity, problems do not resolve with infancy. Like prematurity [64], an increasing body of data now show that children and young adults may need mental and physical support for years after resolution of NAS. Whether this is a result of direct drug effects or is related to the myriad of environmental, genetic and social problems faced by drug-using families is uncertain but cannot be ignored. The complexities of inter and intra personal cannot be divorced from the physical repercussions of NAS [65] and addressing this issue, considering the scope of maternal opioid-use, must be addressed as an urgent global priority to stop the inexorable and intergenerational disadvantage for millions of children around the world.

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