Handling drug misuse in the neonatal unit

Neonatal abstinence syndrome (NAS), a syndrome of newborn drug withdrawal, is increasing in incidence across the developed world. To optimally manage the infant with NAS an integrated multidisciplinary approach is necessary, spanning the intrauterine and postnatal period. Such an approach should incorporate screening for drugs of misuse, early involvement of community services, standardised scoring of NAS symptoms in the drug exposed infant, and the appropriate commencement and monitoring of evidence-based pharmaceutical therapy.

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Key points

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1. Screening methods for substance misuse include maternal history, urinalysis from mother and infant, meconium analysis, and maternal or neonatal hair analysis.
2. Scoring charts can be used to identify those infants meriting active management of their NAS and to facilitate standardised treatment decisions.
3. Since opiates are excreted in breast milk in low concentrations, breastfeeding may lessen the severity of withdrawal symptoms.
4. Involvement of community services from the pre-birth case conference up to and following hospital discharge is essential.

Neonatal Abstinence Syndrome (NAS) is a syndrome of substance withdrawal observed in infants delivered to mothers dependent on physically addictive substances during pregnancy. Symptomatic withdrawal can occur following intrauterine exposure to a variety of different chemical substances. These include the well recognised opiate, barbiturate and benzodiazepine drug classes. Ethanol, caffeine and antidepressants[1] (particularly selective serotonin reuptake inhibitors) can all precipitate symptomatic NAS.

NAS is becoming progressively more common across the developed world. In the United States of America the number of drug-affected newborns increased between the 1980s and the late 1990s by 300%[3]. In the United Kingdom the incidence of drug exposure in newborn infants has been reported to vary between 14 and 90% of live-born infants, with urban and socially deprived areas reporting higher incidences[4]. The most recent Scottish statistics on drug misuse reported an incidence of drug misuse during pregnancy of 6.7 per 1000 deliveries in 2004. Glasgow has well-documented social problems and contains nine of the ten most socially deprived areas in the UK.

In the geographical area served by Princess Royal Maternity Hospital (PRMH) the incidence of symptomatic NAS has risen 10-fold over the last decade, such that 17% of infants admitted to the Special Care Baby Unit (SCBU) are transferred for the management of NAS[5,6]. This increased clinical burden has clear implications for SCBU cot occupancy, nursing resources, mother-infant bonding and healthcare costs within the unit. Consequently, the City of Glasgow has a well-established, integrated, multidisciplinary service for the management of substance misuse during pregnancy, based at PRMH.

Intrauterine exposure to addictive drugs can have short and long term adverse consequences for the offspring. Short term consequences include an increased neonatal mortality from sudden infant death syndrome and symptomatic NAS. The clinical presentation of NAS is varied and affected infants exhibit non-specific symptoms and signs. Common presenting features include irritability, jitters, poor feeding with an uncoordinated suck, and persistent high-pitched crying. Seizures can occur but are uncommon. A degree of clinical suspicion of NAS is therefore important in infants in whom such signs are observed. In the longer term adverse neurodevelopmental outcomes have also been reported: lower verbal and performance IQ and an increased incidence of attention deficit hyperactivity disorder (ADHD) relative to control subjects have been observed[2].

The above introduction highlights the increasing importance of NAS to modern neonatal practice. This article aims to explore the methods used to identify cases of drug misuse during pregnancy, review the evidence underlying appropriate treatments for symptomatic NAS in affected infants, and explore the potential long term consequences for these infants.

Screening for drugs of misuse in pregnancy

In order to optimally manage symptomatic NAS, awareness of the local pattern of drug

misuse is important. Several methodologies can be employed to evaluate the extent of misuse during pregnancy and the specific substances misused. These include a maternal history of substance misuse, urinalysis from the mother or infant, meconium analysis, and maternal or neonatal hair analysis.

The maternal interview technique can significantly underestimate the true incidence of substance misuse during pregnancy. This is particularly the case when a basic interview technique is used rather than a more accurate, but time consuming, specific structured interview such as the Drug Abuse-Screening Test (DAST). An anonymous questionnaire study of women attending London antenatal clinics reported that 11-16% had used at least one illicit substance by the time of booking: cannabis misuse being the most prevalent[7]. However, large-scale epidemiological studies which have compared the reliability of a maternal history relative to biochemical screening methodologies, identified that the actual incidence of drug misuse during pregnancy may be threefold that estimated by maternal history alone[8,9].

Toxicological analysis of urine from the infant, and often the mother, remains the most commonly applied screening methodology for substance misuse in the UK. The technique is cheap, has been extensively utilised, and relies on the ability of the kidney to concentrate the metabolites of illicit substances in the urine to concentrations many times greater than that detected through analysis of plasma. However, urine toxicology has several potential disadvantages[10]. Urinary screening only gives a forty eight hour window of substance exposure pre-delivery, resulting in a high false negative rate reported between 32 and 63%. Additionally, screening failures may result from an inability to collect urine samples: newborns may pass little urine in the first 48 hours of life and urine collection bags, to facilitate sample collection, can produce skin excoriation.

Toxicological analysis of meconium, the first stool passed by a newborn infant, is presently the 'gold standard' methodology for detecting drug exposure during pregnancy. North American epidemiological studies have confirmed the usefulness of meconium analysis[11-13]. Theoretically, all substances that reach the fetal circulation will be deposited in meconium and thereafter can be detected. This includes illicit drugs excreted by the liver into the biliary system and substances excreted into the urine, which are indirectly incorporated into meconium as the fetus repeatedly swallows amniotic fluid, thus incorporating urine into meconium. Fetal swallowing begins at 12 weeks gestation and meconium forms from 14-16 weeks. Deposition of drugs into meconium can therefore occur from 16 weeks' gestation until term, giving a window of the last twenty four weeks of gestation, where exposure to illicit substances can be analysed in detail. The sensitivity and positive predictive value of meconium screening have been reported as 93 and 82% respectively[14].

Hair and nail samples from infants have also been examined for drug metabolites. In the adult, hair grows at a rate of 10mm per month, and drug metabolites are deposited in the growing hair shaft, giving a wide time potential analytical window for the detection of substance misuse[15]. In the newborn, hair first appears during the third trimester, but can often be sparse, which may limit analytical potential. Hair analysis in the newborn remains relatively unstudied to date. A single case report describes the detection of cocaine metabolites in newborn nail clippings in an infant exposed to cocaine *in utero*. Both of these novel methodologies are insufficiently studied for clinical application at present.

Scoring charts

Without the use of a standard method of assessing the infant with NAS, clinicians have been shown to make markedly varied management decisions. Scoring the clinical signs of infant substance withdrawal enables standard decisions to be made about whether pharmacologic management is indicated for symptomatic NAS, and allows an objective approach to increasing or decreasing the dose of any treatment initiated. All scoring charts are subject to a degree of inter and intra observer variability and a recent national survey in the United States reported that only 65% of those units who responded used such a scoring chart[16]. A variety of scoring charts exist, from the simple to the time consuming and complex. The Lipsitz tool is a relatively simple validated method for NAS symptom scoring and is recommended by the American Academy of Pediatrics (AAP)[17]. When using such charts standardisation of the time of scoring should occur relative to feeds (i.e. a hungry baby will score higher than a recently fed baby). Scoring charts are not without limitations. Charts in current clinical use were developed for use within the neonatal period in term infants with opiate withdrawal. Increasingly such charts are being applied to other non-validated clinical scenarios i.e. premature infants, infants exposed to other illicit substances or multiple substances of misuse, or protracted drug withdrawal extending beyond the neonatal period.

Treatment of NAS

In-patient management

Despite the increasing clinical burden of NAS, clinical trial evidence is insufficient to guide the optimal management of the condition. In Glasgow, infants treated for NAS are nursed with their mothers in the routine postnatal ward unless they have additional morbidity, such as prematurity, necessitating transfer to the neonatal unit. Conservative measures such as holding, swaddling and minimal stimulation may suffice if symptoms are mild and non-progressive. As opiates are excreted in breast milk in small concentrations, breastfeeding may potentially lessen the severity of the withdrawal process as well as improving mother-infant bonding[18,19]. Breastfeeding should therefore be encouraged in all mothers in whom HIV infection does not coexist. Where conservative options and breastfeeding fail to suppress symptomatology, as confirmed through the use of a specific symptom scoring chart, treatment with adequate pharmacotherapy is necessary (**FIGURE 1**).

Historically, many pharmaceutical agents have been used as treatments for NAS. These pharmaceutical agents can be subdivided into two major classes: disease modifying drugs and symptom modifying drugs. The former replace the substance from which the infant is withdrawing from, with the latter acting as general central nervous system suppressants which mask symptoms. Agents utilised include clonidine, chloral hydrate, chlorpromazine, opioids, opiates and phenobarbitone[20]. Studies of the pharmaceuticals used to treat NAS can be criticised for their lack of standardisation of outcome measures, problems with randomisation and failure to utilise validated scoring systems to allow standardisation of the commencement,

FIGURE 1 A six week old baby with neonatal abstinence syndrome treated with Oramorph.

dosage alterations and termination of pharmaceutical therapy[20-24]. In addition, little published evidence exists on the long term effects of any of these pharmaceutical treatments and interventions.

The most recent Cochrane Review on the management of NAS concludes that opiate replacement therapy should remain the first line treatment when there is a history of maternal opiate misuse during pregnancy[5,25]. The barbiturate phenobarbitone, a symptom-modifying agent, may have a role as a second-line treatment particularly where infants have been exposed to multiple drugs of misuse[26]. A single small study infers that combination therapy with phenobarbitone and morphine may be superior to morphine alone as a treatment for NAS[27]. However, design limitations prevent definitive conclusions being drawn from this study and application of its observations to the management of NAS would be premature. Evidence suggests that it may be advantageous to commence pharmaceutical treatments for NAS at a high initial dose, thereafter titrating downwards once adequate symptom control has been achieved. Such a strategy may facilitate more rapid symptom suppression and an abbreviated drug withdrawal.

Preparation for hospital discharge

Social worker input is integral to the management of the drug exposed infant, irrespective of whether the infant subsequently develops symptomatic NAS. Risk assessment for child protection and coordination within and between agencies is important from an early stage to address child protection issues. Child protection issues pertinent to the management of NAS have been covered in detail in a recent edition of *Infant* and will not be further explored in this article[30]. All infants that could be discharged to a potentially 'high risk' environment should be immunised against hepatitis B prior to discharge, with subsequent doses administered by the community healthcare team. Follow-up arrangements and referral pathways should be available for the growing number of infants delivered to mothers who are PCR + for hepatitis C virus as well as other associated blood borne viruses.

As the burden of NAS rises, in terms of case numbers, some centres have considered domiciliary treatment of NAS. From a practical viewpoint such service provision would require strict selection criteria and a multidisciplinary approach. Close cooperation between the in-patient team, hospital and community pharmacists, midwifery staff, social workers, general practioners and health visitors is necessary to provide a safe integrated domiciliary service. A recent pilot of a domiciliary NAS service observed a reduced duration of hospital stay with a conversely greater total duration of infant drug therapy[28]. Whether this model of care, which reported excellent maternal adherence with outpatient appointments, is either cost-effective for the National Health Service, or can be replicated in the United Kingdom, remains to be determined.

Long term consequences of NAS

Few studies have followed drug-exposed children beyond the first few years of life, and confounding variables, such as environment and dysfunctional caregivers make it extremely difficult to attribute any differences observed in ability to NAS *per se*. Detailed long term evaluation of children exposed to drugs *in utero* is necessary to determine whether cognitive ability, social interactions and school achievement are detrimentally affected, and to also determine whether specific treatments for NAS have beneficial effects. In addition, long term follow-up of subsequent growth and development, extending into health in adult life is desperately needed. Of the few published reports available Ornoy et al have attempted to dissect whether differences in ability observed in children who had previously experienced NAS, reflect 'nature' or 'nurture'[29]. Children living with heroin-dependent parents were shown to have poorer verbal and performance IQs, poorer reading and arithmetic skills and an increased incidence of ADHD, relative to children of heroin-dependent mothers living with adopted parents, in whom a modest deficit in performance IQs relative to controls was the sole difference observed[29].

Conclusion

To optimally manage NAS it is important to understand local patterns of drug misuse by pregnant women in order to select the most appropriate replacement therapy to treat symptomatic cases of NAS. Although there is limited evidence on optimal treatment, opiate-replacement therapy remains the first-line treatment, with the use of a standardised scoring chart to facilitate objective treatment decisions. A multidisciplinary approach is beneficial for successful outcome and thought needs to be given to the possibility of domiciliary management of carefully selected infants with NAS. Longer term follow-up studies are required to further guide the management of this increasingly prevalent disorder.

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BOOK REVIEW

Feeding and nutrition in the preterm infant

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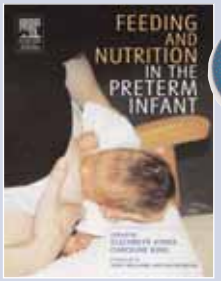

'A practical yet comprehensive guide to best practice in providing optimum nutrition to the preterm infant' – this book does exactly what it says on the back cover – 'ensuring that safe and effective feeding skills are achieved'. Elizabeth Jones and Caroline King deliver a wealth of well-referenced and evidence-based information, having reviewed recent, world-wide research on the subject of preterm infant feeding and nutrition. The subject matter includes the benefits of human milk for the preterm baby, nutritional requirements and ensuring nutritional adequacy of human milk. The authors explain breast anatomy and physiology, milk expression and human milk banking. Enteral feeding, growth and outcome, feeding development and the transition from tube feeding to breastfeeding are described. Case studies illustrate feeding problems, and interventions and outcomes are given. A useful chapter on benchmarking and audit completes the book. Each chapter contains a practical summary of recommendations, allowing for easy digestion of the facts! Photographs, diagrams and drawings are used to good effect within the text.

This book is relevant for all staff working with premature infants, whether in the neonatal unit or following discharge from hospital. The authors include a speech and language therapist and a milk bank manager. The editors, a breastfeeding co-ordinator and a paediatric dietician, are well qualified to produce a book on this subject. Peter Hartmann's ultrasonic research into the anatomy and physiology of lactation updates our understanding of the difficulties that mothers of premature infants face when expressing their breastmilk.

'Feeding and Nutrition in the Preterm Infant' fills a gap in the literature by focussing on the specialised nutritional needs of premature babies who need help in attaining feeding independence. It is a reasonable price for the immeasurable impact that implementation of these recommendations could have on these vulnerable infants.

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