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## Neonatal Abstinence Syndrome: Treatment and Pediatric Outcomes

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### Abstract

Recent rise in rates of opiate replacement therapy among pregnant women have resulted in increasing number of infants requiring treatment for neonatal abstinence syndrome. Short- and long-term developmental outcomes associated with prenatal opiate exposure are discussed, including symptoms and severity of neonatal abstinence syndrome (NAS), and early cognitive and motor delays. Maternal and infant risk factors are discussed, and include patterns of maternal substance use during pregnancy, genetic risk, polysubstance exposure pharmacologic treatment for NAS and breastfeeding. The importance of characterizing corollary environmental risk factors is also considered.

### Keywords

Neonatal Abstinence Syndrome; maternal opiate dependence; pharmacological treatment for opiate addiction; neonatal and long-term developmental outcomes

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The increased incidence of prenatal exposure to opiates reflects the rise in prescription opiate abuse due to changes in pharmacologic availability and diversion, a rapid addiction process, and social factors associated with disadvantage. This phenomenon has particularly affected adolescent and young adult women of reproductive age. Pregnancy is a motivating factor for entry into treatment, but the long-term nature of opiate replacement therapy has grave implications for fetal dependence and postnatal abstinence syndrome sequelae in the newborn. Neonatal and potential long-term outcomes of prenatal opiate exposure are dependent on a complex set of maternal and infant risk and resiliency factors known to impact developmental outcomes. This web of interconnected medical and social determinants will be the focus of this review.

Prescription opiate abuse is epidemic in rural areas such as Maine, West Virginia and Kentucky.<sup>1</sup> According to the 2008 National Survey on Drug Use and Health,<sup>1</sup> psychotherapeutics, including the nonmedical use of prescription narcotics such as

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oxycodone, was the second most reported category of abused illicit substances, behind marijuana. In Maine, opiate abuse disproportionately affects individuals of low socioeconomic status, and is frequently accompanied by polydrug abuse with 40% reporting concurrent problematic alcohol use.<sup>2</sup>

Opiate exposure during pregnancy challenges fetal physiological regulatory systems through fluctuating concentrations of opiates. This may lead to acute episodes of binge and withdrawal in the fetus which has been attributed to the high rates of in utero fetal death.<sup>3,4</sup> To address this risk, stable, daily dosing with methadone in a therapeutic setting is recommended during pregnancy based on the view that fetal withdrawal is better controlled, although fetal distress is suggested by some studies.<sup>5</sup>

## Opiate Replacement Treatment

During pregnancy, methadone treatment programs have successfully lessened use of other opiates and illicit drugs,<sup>6</sup> improved prenatal care, and afforded opportunities to provide psychoeducation.<sup>3</sup> Standard of care for opiate addiction during pregnancy is methadone maintenance treatment (MMT),<sup>7</sup> a harm-reduction treatment approach which reduces illicit drug use, withdrawal symptoms, and craving.<sup>6</sup> Dropout rates of 29% for MMT versus 62% in buprenorphine-maintained patients have been reported.<sup>8,9</sup>

Methadone (6-dimethylamino-4,4-diphenyl-3-heptone) is a synthetic  $\mu$ -opioid receptor agonist. Methadone mimics many of the pharmacological effects of morphine, but with a longer half-life of approximately 24 hours.<sup>10</sup> During pregnancy, doses between 60–100 mg daily are considered therapeutic.<sup>11</sup> During the third trimester, dose increases are typical, and a higher concentration of methadone is transferred across the placental barrier as it becomes more permeable, resulting in reduced maternal plasma methadone concentrations despite an unchanged dose.<sup>14, 6, 15</sup>

Potential long-term effects of prenatal methadone exposure on fetal and infant development are not well characterized. Adverse outcomes result both from direct exposure to illicit opiates and/or therapeutic agents (i.e., methadone), as well as companion interactive and additive effects from co-occurring risk factors (e.g., abuse of alcohol, tobacco, and other prescription medications, socioeconomic status, low levels of education, nutrition and prenatal care, etc.).<sup>16</sup> This is evident, for example, in the Maternal Lifestyle Study which examined infants exposed prenatally to cocaine and opiates. Opiate-exposed infants showed higher orientation scores (i.e., were more alert and attentive) on the NICU Network Neurobehavioral Scales (NNS), as well as deficits in longitudinal follow-up. When adjusted for covariates, there were no independent exposure effects.<sup>16</sup> Exposed infants typically have high environmental risk profiles, and those present at birth are typically stable in the postnatal environment,<sup>18</sup> posing ongoing risk to the developing child. The current view is that environmental risk factors conspire with prenatal exposures to promote epigenetic changes in gene expression and methylation patterns that have both immediate and long-term implications related to developmental programming.<sup>17</sup>

## Neonatal Abstinence Syndrome

Neonatal Abstinence Syndrome (NAS), a direct consequence of MMT during pregnancy. As a withdrawal syndrome, NAS is characterized by dysregulation in central, autonomic and gastrointestinal system functioning.<sup>3</sup> Hallmark CNS features include excessive high-pitched cry, reduced quality and length of sleep following a feeding, increased muscle tone, tremors, and convulsions. These symptoms are accompanied by autonomic dysregulation (e.g., sweating, frequent yawning and sneezing, increased respiration) and gastrointestinal signs (e.g., excessive sucking, poor feeding, regurgitation or vomiting, and loose or watery stools).

Onset of withdrawal symptoms is within 24 and 72 hours after birth<sup>3</sup> and can last up to five days, although we have found that withdrawal symptoms can be present much earlier.

Sustained symptom escalation often requires pharmacological intervention with methadone or morphine. Once NAS symptoms remediate, treatment medication is weaned on a modified protocol that can extend for three weeks or more.<sup>19, 20</sup> Pharmacological intervention is required for 50 to 70% of infants. Whether or not an infant requires treatment is affected by genetic factors, other drug exposures, gestational age, breastfeeding, and rooming-in.

Severity of withdrawal is estimated using various scoring systems, the most common of which is the Finnegan Neonatal Abstinence Severity Score. In general, positive symptoms are given a weighted score and summed every four hours. Decisions regarding treatment onset and rate are made based on a cumulative threshold score,<sup>21</sup> typically two or more consecutive Finnegan scores of eight or nine.

## Predictors of NAS Severity

Many studies report that prenatal maternal methadone dose is unrelated to diagnosis or severity of NAS.<sup>22, 23, 24</sup> Yet, maternal dose, particularly in the third trimester, is associated with longer neonatal hospital stays.<sup>21, 25, 26</sup> Lim and colleagues<sup>29</sup> examined dose in a three group design and found that although gestational age, birth weight, or Apgar scores were not affected, 65% of infants in the low-dose group were treated for NAS, compared with 100% in the high-dose group. For every 5.5mg increase in methadone dose during pregnancy, neonatal length of stay (LOS) increased by one day.<sup>21</sup> In our cohort, maternal methadone dose predicted LOS as did gestational exposure to benzodiazepines.<sup>26</sup>

The duration of drug exposure in utero is an additional factor that dictates severity of withdrawal. Liu and colleagues<sup>25</sup> found that a combination of higher dose before delivery and longer gestational age was associated with NAS treatment, and infants with longer gestation have increased LOS compared to those born with shorter gestation (less than 36 weeks).<sup>24</sup> Longer gestation contributes to NAS severity due to the high permeability of the placental barrier during the third trimester that results in increased levels of fetal methadone exposure nearing delivery.<sup>24</sup> In our cohort, we confirm that MMT is associated with shorter gestation. There are also genetic contributions to need for postnatal pharmacological treatment. Our collaborative effort has revealed single nucleotide polymorphisms (SNPs) of the  $\mu$ -opioid receptor (*OPRM1*, variant A11AG) and catechol-o-methyltransferase (*COMT*) genes affect NAS severity and need for pharmacological treatment. Minor variants were associated with a milder phenotype.<sup>27</sup>

## Factors Associated with Neonatal Outcome

According to some estimates, up to 24% of methadone-maintained infants are born preterm, and 25% are considered SGA (<10<sup>th</sup> percentile for weight).<sup>18</sup> Liu et al.<sup>25</sup> compared infants of opiate-dependent women to those of non-smoking, non-opiate-dependent mothers and smoking, non-opiate-dependent mothers. Birth weights, birth length, and head circumference of infants born to opiate-dependent women were significantly lower than those born to smoking, non-opiate-dependent women, suggesting that opiate exposure, not tobacco exposure, impacts neonatal outcome. Neonatal outcome is impacted by the timing of maternal entry into methadone treatment prior to pregnancy, with earlier entry being associated with more positive infant outcomes. One report<sup>28</sup> examined a sample of methadone-maintained women in terms of gestational point of entry to treatment. Those who entered after 3 months were twice as likely to begin prenatal care after 20 weeks gestation and have infants born prematurely.

Numerous studies indicate breastfeeding decreases NAS severity. Methadone is transferred to the breast milk, but the quantity is negligible and unlikely to account for the decrease in treatment rate by itself. We observed a substantial decrease in neonatal withdrawal severity (decrease in number of infants requiring pharmacological treatment and length of treatment) in mothers who initiated breastfeeding while on methadone, buprenorphine or opiates for chronic pain.<sup>29</sup> We categorized infants as breastfed if the infant received breast milk on day five, even though many women discontinued breastfeeding. Infants that are breastfed have lower Finnegan scores during the first 9 days of life, even after controlling for prematurity and polydrug exposure.<sup>30</sup> In cases when newborns necessitated treatment for withdrawal, the onset occurred later in breastfed infants than in formula fed infants.<sup>30</sup> The initiation and maintenance of breastfeeding is a marker for mothering style which is often accompanied by more maternal contact.<sup>29, 31</sup>

## Long-term Developmental Outcomes

Potential long-term effects of prenatal methadone exposure on infant and toddler development are not known, primarily because of the scientific issue of isolating independent effects of methadone, comorbid substance exposure (e.g., alcohol, tobacco, other illicit drugs) and environmental and medical factors risk factors (e.g., low socioeconomic status, poor prenatal care, severity and treatment for NAS). The increase in opiate-exposed children is becoming a major problem at the interface of healthcare and public policy, yet few studies have used both biological and clinical measures to evaluate developmental outcomes. Published results are older with mixed findings. Hunt et al.<sup>18</sup> assessed opiate-exposed infants at both 18 and 36 months using the Bayley Scales of Infant Development, Second Edition (BSID-II).<sup>32</sup> Mental Development Index (MDI) was significantly lower in opiate-exposed children at 12 and 18 months. Significant differences in birth weight and head circumference between methadone-exposed infants and matched controls showed no BSID-II difference at 6 months of age.<sup>33</sup>

Methadone-exposed infants have been found to exhibit increased motor rigidity, dysregulated motor patterns and decreased activity by observation and maternal report on the Bayley Infant Behavior Record.<sup>34</sup> These motor deficits persisted into toddlerhood and were associated with less social responsiveness, shorter attention spans, and poorer social engagement.<sup>34</sup> Recent studies demonstrate that motor delays are better accounted for by sociodemographic factors.<sup>16</sup> as were birth weight, low quality caregiving, and frequent maternal absenteeism.<sup>16</sup>

In our Maine sample, longitudinal follow-up of methadone-exposed infants has been ongoing with 200 methadone and nonexposed, demographically matched families. Electroencephalographic (EEG) based neurocognitive delays in methadone-exposed one month old infants were found for auditory detection of the positive slow wave response (PSW), an index of working memory updating, when compared to nonexposed infants.<sup>35</sup> When retested at seven months using a similar paradigm, methadone-exposed infants showed recovery of PSW, and were similar to non-exposed, comparison infants.<sup>36</sup> Using the NICU Network Neurobehavioral Scale (NNS), an index of neurobehavioral function at one month of age, methadone-exposed infants displayed deficits in regulation, quality of movement and excitability.<sup>37</sup> At nine months of age, 37.5% of our sample of methadone-exposed infants showed clinically significant motor delays ( 1.5 SD) using the BSID-III compared to low but typical development in the comparison group. Motor deficits were most prominent in the milestones of sitting independently and crawling.<sup>38</sup>

Exposure to other licit and illicit drugs prenatally has been shown to have effects on long-term cognitive and motor outcome. Numerous studies of alcohol-exposed children have

demonstrated hypertonicity and generalized delays in motor functioning during the neonatal period, as well as in older children. Similarly, children who meet diagnostic criteria for fetal alcohol syndrome (FAS) show poor coordination and delayed motor skills, as well as poor visual-motor integration, and delays in fine motor skills, and intellectual ability.

In our Maine sample, methadone-exposed infants who also have a history of alcohol exposure display a different profile than infants with methadone exposure only. At seven months, using the auditory EEG neurocognitive change detection paradigm, methadone-exposed infants who were positive for prenatal alcohol exposure failed to habituate to a novel tone, as determined by high amplitude responding to novelty without decrement over repeated presentations. Methadone-exposed infants without alcohol exposure did not exhibit this pattern.<sup>41</sup> At nine months of age, comorbid alcohol exposure in methadone-exposed infants predicted lower cognitive and language scores on the BSID-III.<sup>41</sup> These results highlight the importance of considering maternal alcohol and tobacco use in evaluating prenatal opiate exposure when determining risk status and treatment considerations in this population.

## Conclusions

Maternal opiate dependence and prenatal fetal exposure present short-term neonatal complications, most notably NAS, but there is very little known about potential opiate dependent effects, either direct or withdrawal related, that could have pre- or early postnatal developmental programming. Further, CNS injury may occur related to iatrogenic medical management of NAS that may be ameliorated by pharmacological optimization and pharmacogenetics. MMT is associated with increased stability of maternal and infant health when compared to illicit opiate use, but long-term developmental effects of methadone are not known. Maternal psychiatric and abstinence support during and after pregnancy, accompanied by early induction into MMT, careful replacement dose titration during pregnancy, consistent prenatal care, and promotion of breastfeeding are recommended interventions to manage the incidence and severity of NAS and mitigate CNS risk. Future early intervention efforts are needed, but must be accompanied by longitudinal developmental monitoring and maternal support.

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