**Journal of Perinatology (2011) 31**, 25–29

www.nature.com/jp

ORIGINAL ARTICLE

# Maternal and neonatal factors impacting response to methadone therapy in infants treated for neonatal abstinence syndrome

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**Objective:** To identify maternal and neonatal factors that impact response to methadone therapy for neonatal abstinence syndrome.

**Study Design:** This is a retrospective review of 128 infants that received pharmacotherapy for opiate withdrawal to identify factors associated with favorable response to methadone therapy. Maternal and neonatal data were analyzed with univariate statistics and multivariate logistic regression.

**Result:** Maternal methadone maintenance dose during pregnancy correlated with length of stay ($P = 0.009$). There was an inverse correlation between the amount of mother's breast milk ingested and length of stay ($\beta = -0.03$, $P = 0.02$). Methadone was initiated later, tapered more rapidly and was more successful as monotherapy in preterm infants. Five percent of infants were admitted to hospital again for rebound withdrawal following reduction of breast milk intake.

**Conclusion:** Severity of neonatal abstinence syndrome may be mitigated by titrating methadone to the lowest effective dose during pregnancy and by encouraging breast milk feeds, which should be weaned gradually.
*Journal of Perinatology* (2011) **31,** 25–29; doi:10.1038/jp.2010.66; published online 27 May 2010

**Keywords:** neonatal opiate withdrawal; phenobarbital; breast milk

## Introduction

Abuse of opiate and addiction to drugs constitute major comorbidities in pregnant women. These women are often transitioned to opiate maintenance therapy with methadone or buprenorphine in an attempt to maintain steady serum opiate concentrations, thereby mitigating drug-seeking behaviors and ameliorating the adverse effect on the fetus.[1–3] Among infants exposed to chronic opiates *in utero*, the incidence of neonatal abstinence syndrome (NAS) ranges from 21 to 94%.[4–6] The onset, duration and severity of NAS may be impacted by the types and degree of fetal drug exposure and by neonatal treatment strategies,[7–13] use of tobacco during pregnancy,[14] gestational age[15,16] and use of maternal breast milk (MBM) as the primary source of nutrition.[17–20] The interactions of these factors and the composite impact on response to pharmacologic therapy for NAS have not been adequately elucidated in a large cohort of infants.

Management of NAS often requires admission to a newborn intensive care unit. However, the specific approach to pharmacotherapy varies between institutions, regarding the ability of mothers to room-in with their infants during birth hospitalization, the provision of nonpharmacologic management,[21–23] the types of follow-up outpatient support systems and the concern that infants may not reliably receive prescribed opiates in the home environment.[6,22,23] The first-line pharmacologic therapy at University Hospital, Cincinnati, is methadone.[17] Phenobarbital is administered as an additional agent if response to methadone is inadequate. Patients are discharged home if they remain free of signs of NAS for 48 h after completion of the methadone taper. Response to the protocol has been variable, resulting in a wide range of duration of therapy and length of hospital stay. Therefore, the objectives of this study were to determine maternal and neonatal factors that are independent predictors of response to methadone pharmacotherapy for NAS.

## Methods

This was a retrospective review of the records of all newborns that received methadone therapy for NAS in the newborn intensive care unit at The University Hospital in Cincinnati, Ohio between January 2002 and December 2007. Infants eligible for this study were identified through the hospital's pharmacy database that was cross-referenced to the 'electronic medication administration record' and nursing flow sheets. Most of the infants (82%) were delivered to mothers that received prenatal care through an affiliated clinic where all patients were managed with methadone maintenance therapy. Other infants were delivered to mothers with

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Received 20 January 2010; revised 15 March 2010; accepted 27 March 2010; published online 27 May 2010

a history of dependence on opiates or had urine drug screen positive for opiates. Mothers were counseled extensively during prenatal visits regarding the benefits of nursing or providing expressed MBM to their infants.

All newborn infants treated with at least one dose of methadone according to the treatment protocol for NAS (described below) were eligible. Infants were excluded from the study if they (1) were treated with other opiate agonists before initiation of methadone protocol, (2) were transferred to another hospital or (3) died before methadone therapy protocol was completed. For the purpose of this study, infants delivered at $\geqslant$37-week post-menstrual age were categorized as 'term infants'. All other infants were classified as 'preterm infants'.

This study was approved by the University of Cincinnati Institutional Review Board.

*Neonatal abstinence syndrome treatment protocol*

Infants delivered to mothers with a history of opiate use or a positive urine toxicology screen are routinely monitored for NAS using the Finnegan abstinence scoring method.[24] All infants included in the study received methadone under a previously published treatment protocol[17] if signs of NAS persisted despite nonpharmacologic management (swaddling, minimal tactile stimulation, dimmed lighting and frequent feedings). Briefly, methadone therapy is initiated at 0.1 mg kg$^{-1}$ orally, every 4 h following two consecutive Finnegan scores greater than eight. Subsequently, there is an eight-step tapered daily dosing regimen, concluding with methadone 0.012 mg kg$^{-1}$ per day. Progression through the protocol is guided by Finnegan scores assessed every 4 h, the goal of which is to achieve scores consistently less than eight. Whenever doses or entire steps are skipped (usually at the physician's discretion due to excessive somnolence), infants are designated as having accelerated the taper. Infants who are unable to progress sequentially through the eight steps due to sustained increase in Finnegan scores ($\geqslant$8) are classified as nonresponders and are treated with concomitant phenobarbital at 10 mg kg$^{-1}$ orally every 12 h for three doses, then 5 mg kg$^{-1}$ daily subsequently.[25] Generally, infants are discharged if they are free of signs of NAS for 48 h after discontinuation of methadone therapy. Nonresponders may be discharged home on phenobarbital, which is weaned, in the outpatient setting, in coordination with the follow-up pediatricians.

*Data acquisition*

Medical records were queried for maternal urine drug screens and maternal self-reported history for methadone (including most recent daily dose), other opiates, cocaine, marijuana, benzodiazepine, barbiturate, selective serotonin reuptake inhibitor and tobacco use. In addition, gestational age, average of two Finnegan scores before the first dose of methadone, age at the initiation of methadone protocol, initial methadone protocol step, instances of acceleration of the taper, instances requiring doses higher than the initial protocol step, adjunctive pharmacotherapy with phenobarbital, length of methadone treatment and hospital length of stay (LOS) were abstracted. Nursing flow sheets were reviewed to determine the proportion of total fluid intake that was comprised of MBM.

*Statistical analysis*

Continuous data were reported as means with standard deviations or medians with ranges. Unadjusted differences for continuous data between preterm and term infants were assessed using the *t*-test or Wilcoxon's sum rank test as appropriate. Differences between categorical data were tested using $\chi^2$-analysis or Fisher's exact test as appropriate. Spearman's correlation coefficients were used to evaluate relationship among factors (continuous variables) associated with response to pharmacologic therapy. To ascertain the independent relationship between variables that were significantly associated with response to methadone therapy in the unadjusted analysis, we constructed a multiple linear regression model. The variable representing LOS was log-transformed as it did not conform to a normal distribution. Variables that were associated with LOS at the $P<0.2$ level were included in the model to avoid inadvertent elimination of potentially important associations. Variables were retained in the model only if their significance level remained at $P\leqslant 0.05$. All statistical analyses were performed with SAS version 9.1 software (SAS, Cary, NC, USA).

## Results

*Patients*

A total of 142 infants were identified as potential study subjects. Fourteen infants were excluded for the following reasons: no documentation of methadone on medical administration record ($n=7$), administration of opiates before initiating methadone protocol ($n=3$), nonadherence with methadone protocol for initial dosing ($n=2$), transfer to another hospital or demise before completion of methadone taper ($n=1$ each). A total of 128 infants representing 1528 methadone treatment days were included in the analyses; 105 (82%) were born to mothers on methadone maintenance therapy. The precise maternal methadone dose was ascertained in 94 (73%) infants. The dose was not disclosed in 23 (18%) mothers because they were enrolled in other studies in the Prenatal Clinic. The remaining 11 mothers were addicted to opiates other than methadone.

*Response to methadone protocol (preterm vs term infants)*

The demographic characteristics of term infants and response to pharmacotherapy are compared with those of preterm infants in Table 1. There were no significant differences in the hospital LOS between neonates exposed to methadone *in utero* compared with infants that were additionally exposed to other classes of drugs including benzodiazepines ($n=17$), barbiturates ($n=7$), cocaine

**Table 1** Pharmacodemographic characteristics

| | *Preterm infants (N = 36)* | *Term infants (N = 92)* | P-*value* |
|---|---|---|---|
| Gestational age (weeks) | 33.6 (2.1) | 38.5 (1.1) | <0.001 |
| Maternal methadone dose (mg per day) | 80.8 (47) | 70.7 (44.7) | 0.33 |
| Other maternal drug use[a] | 26 (72) | 54 (59) | 0.16 |
| Finnegan scores before therapy | 10.5 (2.5) | 11.5 (3.0) | 0.09 |
| Maternal breast milk as source of nutrition[a] | 16 (44) | 59 (79) | 0.08 |
| Age at initiation of methadone therapy (days) | 2.4 (1.6) | 1.8 (1.2) | 0.04 |
| Acceleration of methadone taper[a] | 26 (72) | 42 (46) | 0.007 |
| Duration of methadone therapy (days) | 10.8 (9.5) | 12.4 (8.7) | 0.35 |
| Length of hospitalization (days) | 20.6 (16.5) | 17.3 (9.9) | 0.27 |
| Additional therapy with phenobarbital[a] | 3 (8.3) | 25 (27) | 0.002 |

Continuous variables reported as means (s.d.).
[a]Categorical variables reported as *N* (%).

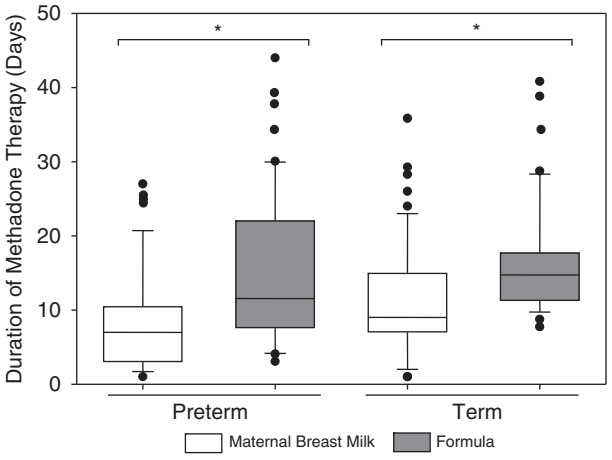


**Figure 1** Duration of methadone therapy for NAS in preterm or term infants and type of feed. Median length of methadone therapy for NAS was compared between preterm and term infants; formula-fed (solid bar) and maternal-breast-milk-fed infants (open bar). *$P<0.04$.

($n = 23$), selective serotonin reuptake inhibitors ($n = 17$), marijuana ($n = 12$), additional opiates ($n = 29$) or tobacco ($n = 98$).

Infants that required adjunctive therapy with phenobarbital were born of mothers on higher doses of methadone (median 90 (0 to 150) vs 60 (0 to 160) mg per day, $P = 0.04$) and they had longer LOS (median 24.5 (12 to 93) vs 13.0 (3 to 43) days, $P<0.0001$) compared with infants managed with methadone monotherapy.

Methadone therapy was initiated at a later time ($P = 0.04$), was accelerated more frequently ($P<0.01$) and was supplemented with phenobarbital less frequently ($P = 0.002$) in preterm infants compared with term infants.

### *Ingestion of maternal breast milk and response to methadone therapy*

During birth hospitalization MBM was at least partially available to 56 (60.8%) term infants. There was no significant association between ingestion of MBM and age at initiation of methadone protocol. MBM feedings were associated with a shorter median duration of methadone therapy in both preterm and term infants (Figure 1). Compared with formula-fed infants, ingestion of MBM was associated with shorter LOS (median 12.5 (3 to 51) vs 18.5 (9 to 43) days, $P = 0.01$). Five (4%) infants who had been on MBM during birth hospitalization were readmitted for NAS within 2 weeks of discharge. On readmission, MBM intake had been either discontinued ($n = 3$) or considerably reduced.

The bivariable (unadjusted) relationship between clinical variables and both length of methadone therapy and LOS was assessed with Spearman's correlation coefficients (Table 2). To further assess the relationship between intake of MBM and LOS, we performed multiple linear regression analysis. The percentage of MBM to total intake was independently associated with LOS

**Table 2** Correlations among determinants of response to pharmacologic therapy for NAS

| | *LOS* | *Maternal dose* | *Finnegan score* | *GA* | *DOL first dose* | *Percent MBM*[a] |
|---|---|---|---|---|---|---|
| Days on methadone | 0.86 | 0.19 | 0.06 | 0.11 | −0.15 | −0.29 |
| | **<0.0001** | **0.07** | **0.54** | **0.23** | **0.10** | **0.005** |
| LOS | | 0.26 | −0.04 | −0.05 | 0.04 | −0.31 |
| | | **0.009** | **0.64** | **0.59** | **0.69** | **0.003** |
| Maternal dose | | | −0.15 | −0.09 | 0.11 | 0.15 |
| | | | **0.14** | **0.38** | **0.28** | **0.18** |
| Finnegan score | | | | 0.19 | −0.26 | 0.08 |
| | | | | **0.04** | **0.005** | **0.46** |
| GA | | | | | −0.18 | 0.07 |
| | | | | | **0.04** | **0.50** |
| DOL first dose | | | | | | 0.03 |
| | | | | | | **0.79** |

Abbreviations: DOL, day of life; GA, gestational age; LOS, length of stay; MBM, maternal breast milk.
The top number in each cell represents the correlation coefficient; the bottom number (bold) represents the *P*-value for the correlation.
[a]Maternal breast milk data on term infants only.

($\beta = -0.03$, $P = 0.02$ for every 10% increase in proportion of MBM intake).

## Discussion

Optimal management of NAS is confounded by inconsistencies in literature reports about maternal and infant approaches to pharmacotherapy, the benefits of feeding MBM, and the differences

in responses between term and preterm infants. Our comprehensive review of the factors that have been implicated to impact response to pharmacotherapy clarifies some of the existing conflicting reports. Our analysis identifies that ingestion of MBM is an independent predictor of response to pharmacotherapy and that maternal methadone dose may be an important determinant of LOS.[9,11] In preterm infants, the onset of NAS was later, pharmacotherapy was tapered more quickly and adjunctive therapy with phenobarbital was required less often compared to term infants.

Several studies of infants fed with milk from mothers on methadone maintenance therapy[17,18,26] suggest reduced incidence and severity of NAS. Our study data affirm that the magnitude of the favorable response correlates with the volume of MBM ingested as a proportion of total intake. On the basis of pharmacokinetics and other reports of concentrations of methadone in human milk from mothers on methadone, we estimate that the intake of methadone exclusively from MBM could be as high as $0.05\,mg\,kg^{-1}$ daily. This may be sufficient to prevent or ameliorate the severity of NAS. Subsequent abrupt cessation of MBM ingestion or rapid weaning could precipitate rebound withdrawal as reported by Malpas and Darlow.[27] Our findings are consistent with this assertion. Future studies identifying infants at risk for rebound NAS, including correlation with serum concentrations, are warranted.

The differences in the pharmacokinetics and pharmacodynamics of methadone in the fetus, preterm or term infants have not been elucidated. Maternal serum and milk methadone concentrations, activity of human milk β-casomorphins, the gestational age of the infant, body adiposity, pharmacogenetics and concomitant disease states are all likely to impact the absorption, distribution, metabolism and excretion of methadone. Response to pharmacotherapy for NAS with paregoric, phenobarbital, or morphine[15,16] differed considerably between preterm and term infants. Similarly, in this report, preterm infants responded more favorably to methadone therapy. The wide ranges of duration of pharmacotherapy and lengths of stay during birth hospitalization, together with the majority of infants accelerating the methadone taper protocol, suggest that the methadone doses prescribed may be safely lowered. Care providers should aim for a more individualized approach to initial methadone dosing, which takes into consideration the gestational age and the availability of MBM as primary nutrition, to expedite discharge of infants with NAS. Validation of this approach is warranted.

One of the limitations of our retrospective study is incomplete data collection from the medical records. For instance, the number of infants that were rehospitalized for withdrawal symptoms may have been underestimated. The Finnegan abstinence scoring method is a subjective assessment of NAS designed for term infants and may not be sensitive in detecting the manifestation of NAS in preterm infants. Owing to our emphasis and focus on the benefits of MBM in treating NAS, there might have been a degree of bias in initiating therapy at a lower dose and more aggressive weaning of infants fed MBM, possibly contributing to earlier discharge. These should be taken into consideration in interpreting our findings.

In summary, in addition to the well-established nutritional and immunologic benefits, ingestion of MBM may be an independent predictor of favorable response to methadone therapy for NAS. Further studies are needed to identify infants at risk for rebound NAS. Our study data indicate that opiate requirements in preterm infants with NAS are less than in term infants. In conclusion, a coordinated management care plan for opiate-dependent women beginning early in pregnancy, which outlines the risks of fetal drug exposure, emphasizes the benefits of providing MBM to infants, and cautions against rapidly weaning infants from MBM may reduce the public health burden posed by NAS.

## Conflict of interest

The authors declare no conflict of interest.

## Acknowledgments

We acknowledge the staff of the Department of Pharmacy at The University Hospital for their support, especially Monica Commins, and to Laura Gerlacht, Eric Mueller and Steven Hoath for critical review of the article.

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