Relationship between Maternal Methadone Dose at Delivery and Neonatal Abstinence Syndrome

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Objective To estimate the relationship between maternal methadone dose and the incidence of neonatal abstinence syndrome (NAS).

Study design We performed a retrospective cohort study of pregnant women treated with methadone for opiate addiction who delivered live-born neonates between 1996 and 2006. Four dose groups, on the basis of total daily methadone dose, were compared (≤80 mg/d, 81-120 mg/d, 121-160 mg/d, and >160 mg/d). The primary outcome was treatment for NAS. Symptoms of NAS were objectively measured with the Finnegan scoring system, and treatment was initiated for a score >24 during the prior 24 hours.

Results A total of 330 women treated with methadone and their 388 offspring were included. Average methadone dose at delivery was 117 ± 50 mg/d (range, 20-340 mg/d). Overall, 68% of infants were treated for NAS. Of infants exposed to methadone doses ≤80 mg/d, 81-120 mg/d, 121-160 mg/d, and >160 mg/d, treatment for NAS was initiated for 68%, 63%, 70%, and 73% of neonates, respectively (P = .48). The rate of maternal illicit opiate abuse at delivery was 26%, 28%, 19%, and 11%, respectively (P = .04).

Conclusion No correlation was found between maternal methadone dose and rate of NAS. However, higher doses of methadone were associated with decreased illicit opiate abuse at delivery. *(J Pediatr 2010;157:428-33)*.

Methadone has been used since the early 1970s to treat opiate addiction, and it currently remains the standard treatment for opiate addiction in pregnancy.[1] Benefits of methadone include a reduction in cravings for heroin and drug-seeking behavior, which also reduces the risk of infection with hepatitis C virus and human immunodeficiency virus (HIV), prostitution, and criminal activity.[2] Methadone treatment also protects the fetus from repeated episodes of withdrawal by providing steady maternal opiate levels.[3] Furthermore, comprehensive methadone maintenance programs provide opiate-addicted women with the opportunity to receive essential prenatal care and services that they would otherwise be without.[4] Despite these benefits, methadone treatment is not without controversy, and much of the debate centers on the optimal methadone dose and on its association with neonatal abstinence syndrome (NAS).

One of the earliest reports of the relationship between methadone and neonatal withdrawal was published in 1975 by Rosen et al. The authors found no consistent relationship between maternal methadone dose and the severity of neonatal withdrawal symptoms in this study and a subsequent study in 1976.[5,6] In the same year, several studies reported the opposite, showing a positive correlation between maternal methadone dose and both the severity of neonatal withdrawal symptoms and the incidence of neonatal withdrawal requiring pharmacologic treatment with maternal methadone doses <20 mg/d.[7-9] Of 8 published studies, which include a "low" dose group of <30 mg/d, 78% report a positive correlation between maternal methadone and NAS.[6-13] Presently, methadone maintenance programs for pregnant women use significantly higher doses to prevent withdrawal. Five of 6 more recent studies that use a higher cutoff point (<50 mg/d or above) to define the "low" dose group report no such association.[14-19] However, despite these and other studies,[20-25] there is still no clear answer. Much difficulty is caused by the considerable methodological variability, such as the inclusion of women undergoing withdrawal treatment as opposed to maintenance treatment, insufficient reporting of confounding factors (ie, polysubstance abuse), and differences in the definition and assessment of NAS (Table I; available at www.jpeds.com). With these limitations in mind, our objective was to estimate the relationship between clinically appropriate methadone doses and NAS.

Methods

We performed a retrospective review of the outcomes of opiate-addicted women receiving methadone maintenance who delivered live-born neonates between

HIV	Human immunodeficiency virus
NAS	Neonatal abstinence syndrome
OR	Odds ratio
ROC	Receiver operating characteristic
SSRI	Selective serotonin reuptake inhibitor

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September 1996 and June 2006. A full description of our approach to methadone stabilization and maintenance was described previously.[14] The only change in maternal management in the 11-year study period was a small increase (20 mg to 30 mg) in the initial stabilization dose. There were no changes in neonatal assessment or treatment for NAS. No distinction was made between women who conceived while already enrolled in a methadone program and women who became pregnant while taking heroin and required initial stabilization during pregnancy.

All neonates were delivered at Thomas Jefferson University Hospital. We excluded infants delivered <32 weeks gestation, because signs and symptoms of prematurity can be confused with NAS.[21] Signs and symptoms of NAS were objectively assessed every 8 hours for the first 72 hours of life as described by Finnegan.[25] Treatment for NAS was initiated for a cumulative score ≥24 during the earlier 24 hours. Our NAS treatment protocol has been previously described.[26] Data for a portion of the women and neonates were previously reported.[14,26]

Exposure to methadone was confirmed with a urine drug screen for methadone. For women who instead had a drug of abuse screen (does not test for methadone), documentation in the medical record of methadone use was necessary for inclusion. The methadone dose at delivery was defined as the total daily methadone dose at the time of delivery. To determine the cohorts, we divided women in 4 dose groups approximating quartiles; ≤80 mg/d, 81-120 mg/d, 121-160 mg/d, and >160 mg/d. A receiver operator characteristic (ROC) curve was used to determine the sensitivity and specificity of various methadone dose cutoff points for predicting NAS, ensuring the appropriateness of these dose groups.

All statistical tests were performed with SPSS software version 17.0 (SPSS Inc., Chicago, Illinois). The χ^2 test, analysis of variance test, and Kruskal-Wallis test were used to analyze categorical, normally distributed continuous, and non-normally distributed continuous variables, respectively. A P value <.05 was considered to be statistically significant. Several women delivered twice during the study period. To adjust for potential confounding and clustering caused by women who had >1 pregnancy during the study period, a generalized estimating equation model was used.

For women who delivered after 2000, the database was expanded to include additional variables. The additional information included non-opiate illicit drug abuse at delivery as determined with a urine drug screen, SSRI use, alcohol use (by self-report), and others. Because of the difference in the number of variables, 2 separate multivariate models were fit. The first was termed "limited" in time because it included a larger set of variables that were recorded only for women who delivered between January 2000 and June 2006. The second was deemed "extended" in time because it included fewer variables, but data were available for all women who delivered during the entire 11-year study period (September 1996 to June 2006). For both the "limited" and "extended" adjustments, variables with $P < .2$ found through univariate analysis were included as covariates in the generalized estimating equation model to calculate adjusted odds ratios (OR) with 95% CIs. This study was approved by the Thomas Jefferson University Institutional Review Board. Informed consent was not required.

Results

We analyzed outcomes of 330 opiate-addicted women receiving methadone treatment who had 386 pregnancies from September 1996 to June 2006. Two women had twins, thus our study included 388 neonates. The gestational age at birth was <32 weeks for 19 neonates (range, 27-31 weeks) excluded from the study. Maternal demographic characteristics are presented in **Table II**. Only race differed between dose groups (P = .04). Caucasian women were receiving higher mean doses of methadone (123 ± 51 mg/d) when compared with non-Caucasian women (104 ± 45 mg/d, $P < .001$). Psychiatric medications were prescribed to 27% of women in the methadone maintenance program, and 23% of those women were taking >1 psychiatric medication (data available for 288 pregnancies). The proportion of women in each dose group using prescription psychiatric drugs was not significantly different (P = .39), but prescription benzodiazepine use (mainly clonazepam) was more common in women receiving higher doses (P = .01).

Details of the methadone maintenance program and rates of illicit substance abuse at the time of delivery are shown in **Table III**. Overall, the average methadone dose at delivery was 117 mg/d (range, 20-340 mg/d). Timing of methadone stabilization (before or during pregnancy) and rate of re-stabilization (because of non-compliance) was known for 288 pregnancies. Women who conceived while taking methadone had a higher mean methadone dose at delivery compared with women who were stabilized during pregnancy (135 ± 56 mg/d versus 119 ± 49 mg/d; P = .01), and a greater proportion of women who conceived while taking methadone were in higher dose groups. Admissions for re-stabilization were less likely in the higher dose groups, as was illicit opiate abuse. Of the 77 women with known prescription psychiatric medication use, 27 (35%) used illicit drugs at delivery, compared with 42 (20%) of the 211 women not taking prescription psychiatric medications (P = .008). Women who were initially stabilized on methadone during pregnancy had lower rates of illicit drug abuse at delivery (66 [34%] versus 26 [28%]; P = .36) and illicit opiate abuse at delivery (11 [12%] versus 36 [18%]; P = .17), but the difference did not reach statistical significance.

Neonates had an average gestational age at delivery of 37.7 ± 2.2 weeks. The rate of preterm birth (≥32 weeks and <37 weeks) was 27% (106/388). The mean birth weight and head circumference were 2808 ± 544 g and 32.5 ± 2.1 cm, respectively. No significant differences were found among gestational age at delivery, birth weight, head circumference, and rate of preterm birth in neonates exposed to maternal methadone doses of ≤80 mg/d, 81-120 mg/d, 121-160 mg/d, and >160 mg/d (all $P > .31$).