



## High-dose methadone maintenance in pregnancy: Maternal and neonatal outcomes

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### KEY WORDS

Methadone  
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**Objective:** This study assesses the effect of higher doses of methadone during pregnancy on maternal and fetal outcomes.

**Study design:** We retrospectively reviewed clinical data for 81 mothers who received methadone and their 81 offspring. The cohort was divided into high-dose ( $\geq 100$  mg) and low-dose ( $< 100$  mg) groups.

**Results:** There were no differences in the rate of medication treatment for neonatal abstinence symptoms or days of infant hospitalization between the high-dose (mean, 132 mg) and low-dose (mean, 62 mg) groups. Despite longer histories of opiate abuse, the high-dose group had less illicit drug use at delivery. The whole cohort, which received an average of 101 mg/d, had an 81 % rate of negative toxicology screens at delivery.

**Conclusion:** High doses of methadone were not associated with increased risks of neonatal abstinence symptoms but had a positive effect on maternal drug abuse. Arbitrarily limiting methadone dose as a way of minimizing the risks of neonatal abstinence symptoms may be unwarranted.

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Methadone maintenance treatment in opiate-addicted pregnant women reduces maternal morbidity and mortality rates and promotes fetal stability and growth, compared with mothers who use heroin. 1,2 Methadone is associated with better compliance with obstetric care and better preparation for parenting responsibilities.<sup>1</sup> The baby, however, is at risk for symptoms of neonatal abstinence syndrome (NAS) that is associated potentially with withdrawal from methadone at birth. Absti

nence symptoms can occur in gastrointestinal, metabolic, and neurologic domains. Mild symptoms may not require medication treatment, although moderate or severe symptoms usually require medication-assisted withdrawal and 3-5 weeks of hospital monitoring.

There are conflicting studies on whether the higher methadone doses that are often needed to eliminate maternal withdrawal symptoms and drug abuse may increase the level of fetal pharmacologic dependence, potentially leading to more severe NAS.<sup>4-9</sup> Berghella et al,<sup>10</sup> in a retrospective review of 100 women maintained on methadone during pregnancy, found no difference in severity, duration, or treatment of NAS between

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infants of mothers who received <80 mg/d of methadone and those who received  $\geq$  80 mg/d. In contrast, Dashe et al,<sup>11</sup> in their retrospective review of 70 women (mean dose, 20 mg/d) who were withdrawn or tapered just before delivery, found significant correlations between methadone dose and NAS.

Therapeutic response to methadone is dose related. Higher doses are associated with the better treatment outcomes in nonpregnant patients, and federal guidelines recommend increasing methadone doses in pregnant patients with withdrawal symptoms.<sup>7-15</sup> Pregnant patients have required 50 to 150 mg/d to suppress withdrawal symptoms.<sup>6</sup>

We retrospectively reviewed mothers and infants in a specialized methadone maintenance pregnancy program with individualized dosing to assess whether higher doses of methadone were associated with adverse neonatal outcomes.

## Material and methods

The study's narcotic treatment program maintains an active census of approximately 1100 methadone maintenance patients in a California metropolitan area with a population of 1.5 million. It is the only specialized provider of pregnancy services for opiate-addicted women in the area. Women in the program are assigned to a specially trained counselor, are all linked with obstetric care, and give written consent for providers to share information. All of the women participate in and receive a psychiatric assessment, supportive psychotherapy, 1 hour of individual drug treatment counseling per week, and participate in a weekly support group for both pregnant and early postpartum patients. All patients provide random weekly urine drug screens. As part of the clinic's on-going quality assurance program, maternal and infant data are collected from program entry until 1 month after delivery.

Patients were maintained on divided doses of methadone, given twice or occasionally 3 times a day, because the sustained plasma levels that are achieved with split dosing are associated with fewer withdrawal symptoms and less illicit drug use during pregnancy.<sup>7,18</sup> As a quality control measure, methadone trough serum levels are measured after women reach stable methadone dosing and are repeated in patients who require unusually high doses. Although there is a therapeutic range for methadone trough levels in nonpregnant patients of 150 to 600 ng/mL,<sup>19</sup> there is no attempt to achieve "target" serum levels. Methadone doses are clinically adjusted, without arbitrary limits, in response to illicit opiate use, withdrawal symptoms, or side effects.

NAS was evaluated with an objective scoring system,<sup>20</sup> and treatment of the infant was initiated clinically when repeated scores were in the 6 to 8 range.

The study was approved by the University of California, Davis, Institutional Review Board. SPSS software (version 11.5; SPSS Inc, Chicago, Ill) was used for all analyses, and probability values  $>.05$  were selected for statistical significance. Data were analyzed with independent samples (between-subjects) 2-tailed t-tests, chi-squared analyses, and Mann-Whitney tests.

## Results

There were 94 admissions to the pregnancy program from February 1999 to May 2003. Thirteen subjects were excluded: 4 women miscarried; 3 women decided to terminate pregnancy; 2 women left treatment; 2 patients requested to taper off methadone, and 2 patients had unavailable outcome information. Eight women had 2 pregnancies during the study; each pregnancy was considered a separate admission. Data were analyzed for 81 admissions and 81 offspring.

The study group was 64% white, 25% Mexican/Hispanic, 6% African-American, 4% Asian, and 1% other. The average maternal age on admission was  $32 \pm 6.4$  years. The average age of first opiate use was  $23 \pm 5.6$  years, and the average years of use was  $10 \pm 6.5$  years. Twenty-five admissions had conceived while on methadone maintenance. All others ( $n = 56$  women) were acutely addicted to heroin ( $n = 49$  women), prescription opiates ( $n = 5$  women), or opium ( $n = 2$  women). Seventy-seven percent of the women were cigarette smokers, with 28% of the smokers using  $> 1$  pack/day. Polydrug abuse (alcohol, cocaine, methamphetamine, or marijuana) was reported by 38% of the women on admission. Seventy-eight percent ( $n = 1188/1528$  specimens) of all maternal urine toxicology screens before delivery were negative for illicit drugs.

The average maternal methadone dose at delivery was 101 mg/d (range, 14-190 mg/d). Trough serum methadone levels were obtained at different gestational ages on only 59 of 81 women during pregnancy because of the difficulty of peripheral venous access in heroin injectors. The mean trough serum level was 146 ng/mL (median,  $115 \pm 101.5$  ng/mL; range, 20-478 ng/mL). Forty-six percent of mothers nursed their babies. The Figure shows the number of babies who were treated for NAS at each maternal dose range.

The infants had a mean gestational age at delivery of 37.3 weeks and a mean birth weight of 2792 g. No major developmental abnormalities were noted. Eighty-one percent of infant toxicology screens ( $n = 66/81$  screens) at the time of delivery were negative for illicit drugs. The 15 positive screens detected opiates ( $n = 4$  women), amphetamines ( $n = 9$  women), cocaine ( $n = 4$  women), diazepam ( $n = 2$  women), marijuana ( $n = 1$  woman), and alcohol ( $n = 7$  woman). Six infants tested positive for 2 drugs. Thirty-seven babies (46%) required

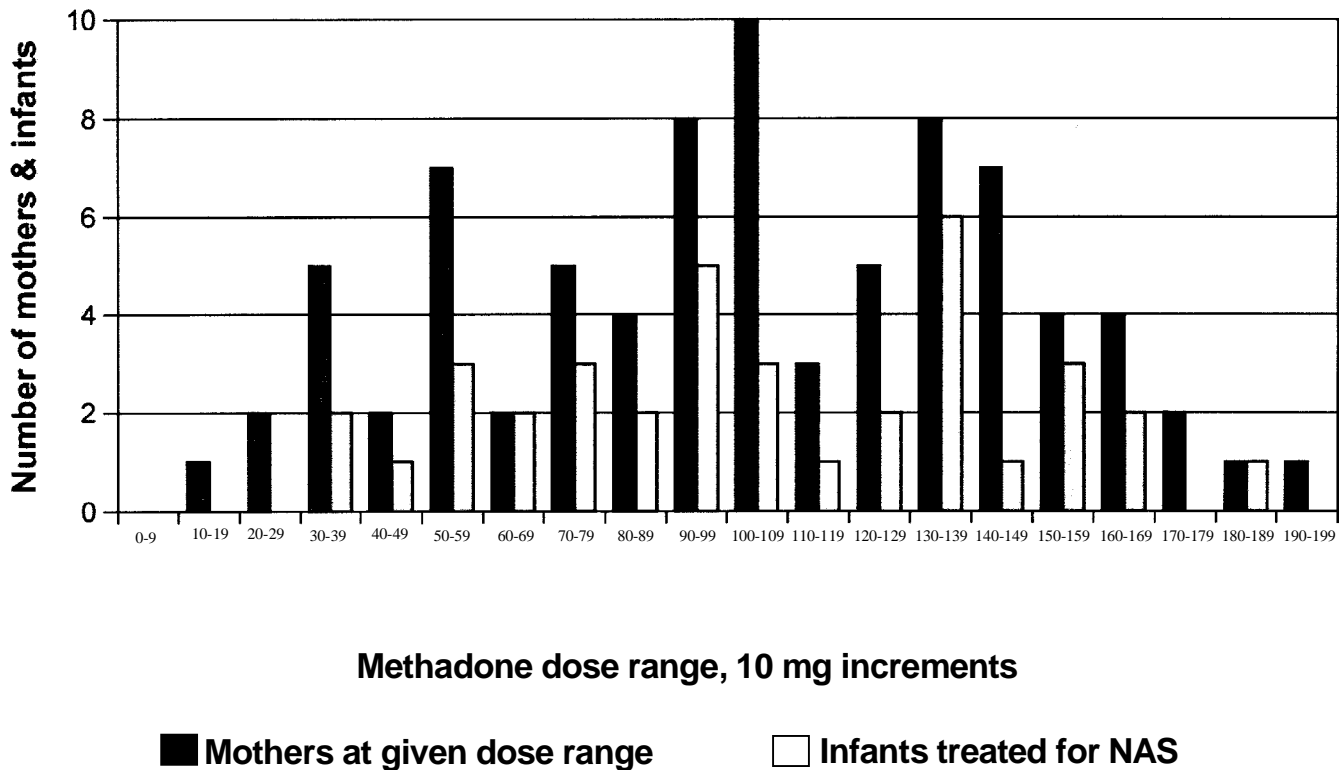


Figure Number of infants who were treated for NAS, by maternal dose range.

medication for treatment of NAS symptoms. Infants were treated with paregoric (n = 20 infants), phenobarbital (n = 10 infants), both paregoric and phenobarbital (n = 4 infants), methadone (n = 1 infant), ativan (n = 1 infant), and both paregoric and ativan (n = 1 infant).

Because of custody issues, length of stay information was not available on 10 infants. The median length of stay for the 71 infants on whom data were available was 10.0 days (range, 1-105 days). There was no significant correlation between maternal dose and length of stay (Pearson correlation co-efficient, .066;  $P = .586$ ). When divided into NAS-treated (n = 37 infants) and untreated (n = 44 infants) groups, the untreated babies spent a median of 3 days (range, 1-44 days) in the hospital, while babies who were treated for NAS spent a median of 25 days (range, 8-105 days). We observed no cases of post-hospitalization NAS in untreated babies during the 1-month postpartum period.

To assess whether higher doses resulted in increased risks of NAS, the cohort was divided into 2 dose groups: mothers who were treated with < 100 mg of methadone (n = 36 mothers) and mothers who were treated with  $\geq$  100 mg (n = 45 mothers). The cut-off of 100 mg for the groups was chosen to achieve approximately equal cohort size. Comparison of maternal dose groups revealed a mean dose in the  $\geq$  100-mg group of 132 mg and 62 mg in the <100-mg group. Independent samples t-tests showed no significant differences between

groups in maternal age, age of onset of drug use, or time in treatment, although the high-dose group had significantly longer histories of opiate abuse (mean, 11.6 years vs 7.8 years in the low-dose group;  $t = -2.6 \pm 66.6$ ;  $P < .05$ ). Chi-squared analyses showed no significant differences between groups in ethnicity, polydrug use history, and smoking history.

The Table shows infant outcome data by maternal dose group. Chi-squared analyses revealed that the higher dose group had significantly less drug use at delivery: 11 % of infant toxicology screens were positive for illicit drugs in the high-dose group versus 27% positive screens in the low-dose group ( $P = .05$ ). There were no significant differences in the incidence of treated NAS between infants of high- and low-dose methadone mothers; 51 % of the high-dose babies and 49% of the low-dose babies required treatment. Mann-Whitney tests for non-normal distributions revealed no significant differences in gestational age ( $U = 735$ ;  $N_1 = 36$ ;  $N_2 = 45$ ;  $P = .47$ ), birth weight ( $U = 775$ ;  $N_1 = 36$ ;  $N_2 = 45$ ;  $P = .74$ ), or days of infant hospitalization ( $U = 600$ ;  $N_1 = 31$ ;  $N_2 = 40$ ;  $P = .81$ ) between high- and low-dose groups.

#### Comment

This retrospective records review of methadone-maintained pregnant women and their offspring found no evidence of an increased incidence of adverse outcomes in babies who were exposed to higher, clinically determined

Table Infant outcomes by maternal	methadone dose group		Maternal methadone dose group	P value
	All (n=81)	>_ 100 mg/d (n = 45)		
Maternal dose (mg/d) <sup>†</sup>	101 ± 42.4	132 ± 24.1	62 ± 24.3	.08 <sup>†</sup>
Gestational age (Wk) <sup>*</sup>	37.3 ± 3.1	37.1 ± 2.9	37.2 ± 3.3	.47 <sup>‡</sup>
Birth weight (g) <sup>*</sup>	2792 ± 694.6	2795 ± 693	2787 ± 687	.74 <sup>‡</sup>
Infants treated for NAS (n)	37 (46 <sup>°/°</sup> )	19 (51%)	18 (49%)	.32 <sup>§</sup>
Positive infant toxicologic result (n)	15 (18 <sup>°/°</sup> )	5 (11 <sup>°/°</sup> )	10 (27 <sup>°/°</sup> )	.05 <sup>§</sup>

\* Data are given as mean ± SD.

† Independent samples t-test.

‡ Mann-Whitney test.

§ Chi-squared test.

methadone doses. The rate of treatment for NAS and length of infant hospitalization was similar for both high-dose (mean, 132 mg/d) and low-dose (mean, 62 mg/d) groups that were studied. Our results extend the findings of Berghella et al<sup>10</sup> to higher average dose ranges.

Importantly, our high-dose group had significantly less detected illicit drug use at delivery, even though this group had significantly longer histories of addiction. Berghella et al<sup>10</sup> found a trend toward less drug use at doses of >\_ 80 mg. Our study suggests that, as in nonpregnant populations, higher doses of methadone do lead to less drug use.<sup>1, 3</sup> Any theoretic goal of reducing NAS by using low doses or tapering schedules may well be off-set by the adverse effects of more illicit drug use. For example, Brown et al<sup>11</sup> reported on a low-dose methadone-treated pregnant population (41 % were maintained on <50 mg) in which 84% of newborn infants tested positive for illicit drugs at the time of delivery, which led them to question the efficacy of methadone treatment.

The dose range (14-190 mg/d) in our cohort was quite wide, possibly reflecting individual differences in methadone metabolism.<sup>21</sup> Accelerated methadone metabolism and decreases in methadone bioavailability occur during pregnancy.<sup>22,23</sup> Consistent with these metabolic effects, the mean maternal methadone serum level during pregnancy in this study was in the low range for methadone, despite the high average dose.

The overall 46% rate of treated NAS for the infants is comparable to, or better than, studies in which lower doses were used. Doberczak et al<sup>15</sup> reported a 78% rate of treated NAS, where the average maternal dose was 50 mg/d. The overall rate of treatment in the Dashe et al<sup>16</sup> study (median, 20 mg/d) was 46%.

We used treated NAS as an outcome measure. We did not assess other variables that might affect the severity of NAS because our study relied on readily available measures that were used in routine clinical practice. Doberczak et al<sup>15</sup> found that the severity of NAS was related to the decline of the neonatal plasma methadone level from day 1 to day 4 of life. Kushel et al<sup>19</sup> confirmed this finding and further found that both low maternal and

low cord methadone concentrations at delivery were associated with more severe NAS. These studies underscore the importance of infant variables in the determination of the risks of NAS. Furthermore, almost one half of our mothers nursed their babies. Methadone levels in milk are small and normally not sufficient to prevent NAS.<sup>24</sup> However, Ballard<sup>25</sup> found that frequent small feedings in the neonatal period were associated with reduced symptoms of NAS. Finally, it is speculative, but the more stable serum levels that are achieved by split doses may have some protective effect against NAS. Mothers who receive inadequate doses of methadone or single-dose regimens often experience repeated episodes of withdrawal, which could possibly sensitize the fetus to the withdrawal state. Further study of the effect of split doses of methadone on NAS is warranted.

The role of non-opiate fetal drug exposure (alcohol, cocaine, amphetamine, and benzodiazepine) in effecting the expression of NAS has not been studied systematically and remains a potential confounder in our study, as in others<sup>4-9</sup>

Maternal recovery from illicit drug abuse is critical for the long-term health and safety of both the mother and the child. The use of adequate doses of methadone during pregnancy in a specialized program such as the one described in this study can increase the likelihood of the mother achieving recovery early in treatment. Continued methadone maintenance after delivery may further reduce the risks of maternal relapse during the critical and often

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