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Association of methadone dose with substance use and treatment retention in pregnant and postpartum women with opioid use disorder

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ABSTRACT

Background: In non-pregnant individuals being treated for opioid use disorder (OUD) with methadone, doses ≥60 mg per day are associated with improved treatment retention and decreased illicit opioid use. Although methadone remains the first line treatment for OUD in pregnant women, there are no studies replicating this finding in pregnancy.
Methods: We conducted a retrospective cohort study of 189 pregnant women treated with methadone for OUD from 2006 to 2013. Chart data collected included demographics, pregnancy dates, methadone doses, and urine drug screen (UDS) results.
Results: Treatment retention at delivery was significantly higher for subjects taking ≥60 mg of methadone (90.1% v. 74.1% $p < 0.005$), as was treatment retention at 60 days postpartum (71.6% v. 37.0%, $p < 0.0001$). Percent of UDS results negative for illicit substances during pregnancy was also significantly higher for subjects taking ≥60 mg (71.5% v. 58.0%, $p < 0.04$). There was no significant difference in UDS results in the first 60 days postpartum (63.9% v. 68.1%). Generalized linear models showed a significant positive relationship between methadone dose and treatment retention at delivery ($p < 0.02$) and at 60 days postpartum ($p < 0.004$) as well as a significant positive relationship between length of time in treatment and treatment retention at delivery ($p < 0.04$) and at 60 days postpartum ($p < 0.007$). Maternal age and percent of negative UDS results were not predictive of treatment retention in either model and there was no significant interaction effect between methadone dose and percent negative UDS results.
Conclusions: In this cohort, women taking ≥60 mg of methadone during pregnancy were more likely to remain in treatment and to provide urine samples negative for illicit drugs. Multivariate modeling suggested a dose dependent response across the entire dose range, rather than a threshold effect at 60 mg.

1. Introduction

Medication assisted treatment with methadone (MAT-M) is internationally recognized as the first line treatment of opioid use disorder in pregnant women (American College of Obstetricians and Gynecologists, 2012; World Health Organization, 2014). Pregnant women in MAT-M have better maternal and fetal outcomes than pregnant women with opioid use disorder who are not enrolled in treatment (Burns, Mattick, Lim, & Wallace, 2007; Doberczak, Thornton, Bernstein, & Kandall, 1987; Hulse, Milne, English, & Holman, 1997). Alterations in metabolism and circulating blood volume impact the effectiveness of methadone treatment and often require dose titration during and after pregnancy (Ordean, Kahan, Graves, Abrahams, & Boyajian, 2013; Wolff, Boys, Rostami-Hodjegan, Hay, & Raistrick, 2005). Although research suggests that the dose of methadone a woman receives during pregnancy is not associated with development of neonatal abstinence syndrome in the newborn (Cleary et al., 2010; Jones, Jansson, O'Grady, & Kaltenbach, 2013), some providers continue to encourage treatment with the lowest dose of methadone possible in the hopes that this will reduce the risk of neonatal abstinence syndrome (Wilder & Winhusen, 2015).

Because longer duration of treatment during pregnancy is associated with better fetal outcomes (Peles, Schreiber, Bloch, Dollberg, & Adelson, 2012), retention of pregnant patients in MAT-M is particularly important (Bao et al., 2009). In the general population, higher doses of methadone are predictive of better treatment retention and less use of illicit opioids, particularly at methadone doses >60 mg (Bao et al., 2009; Faggiano, Vigna-Taglianti, Versino, & Lemma, 2003; Fullerton et al., 2014). There have been few studies of treatment retention in pregnant and postpartum women and it is unknown whether methadone dose affects treatment retention or illicit drug use in this group of patients. The purpose of this study was to examine the relationship between dose, treatment retention, and illicit drug use in pregnant and postpartum women.

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2. Methods

2.1. Clinic description

Subjects in this study were enrolled in a university-affiliated MAT-M clinic with a census of approximately 450 individuals. The clinic is one of the main referral sites for opioid dependent pregnant women seeking MAT-M in the city. The clinic provides daily methadone dosing, weekly individual counselling, biweekly physician appointments with dose adjustments, and coordination of care with prenatal care providers for all pregnant patients. No prenatal treatment is provided at the clinic itself. Random observed urine drug testing is completed approximately every 2 weeks for pregnant patients. The urine drug screens (UDS) include immunoassays for alcohol, amphetamines, barbiturates, benzodiazepines, cocaine, morphine, oxycodone, propoxyphene, PCP, THC, and methadone (and its metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine). Urine temperature and creatinine are monitored. For the purposes of this study, a UDS was considered "negative" if it contained only methadone and methadone metabolites, and had a collection temperature and creatinine within the normal range defined by the test. Clinically, patients with "positive" UDS are encouraged to engage in additional treatment but patients are not discharged for continued drug use. The clinic has an affiliation with several local residential treatment programs so individuals in residential treatment continue to receive their methadone dose daily at the MAT-M clinic.

2.2. Chart review

We used a previously established database containing information on all clinic patients who were pregnant between 1/1/2006 and 10/1/2013 to identify subjects for this study. Variables of interest included patient age, race, ethnicity, outcome of pregnancy (elective abortion, miscarriage, perinatal demise, or live birth), delivery date or termination of pregnancy date, duration of treatment episode, discharge date, and reason for discharge. Only pregnancies resulting in a live birth were included in this study sample. If subjects had multiple pregnancies, we included data only from the first reported pregnancy resulting in a live birth. If subjects had transferred to the clinic on a stable dose from another MAT-M clinic ($n = 7$), they were included in the sample regardless of their duration of treatment in the clinic; otherwise, subjects were only included if they had been enrolled in the clinic for at least 30 days prior to delivery. Subjects were excluded from analysis if they moved prior to delivery ($n = 2$), transferred to another clinic prior to delivery ($n = 11$), had <14 days on the same dose of methadone prior to delivery ($n = 12$), or were still pregnant at the end of the study period ($n = 9$). We conducted a chart review of identified subjects to determine: 1) date of first documentation of pregnancy (via documentation in progress notes or documented urine pregnancy test results), 2) average daily methadone dose while pregnant (defined as the average daily dose of methadone from first documentation of pregnancy until date of delivery or dropout, whichever came first), and 3) all UDS results (positive for any illicit substance vs. negative for all illicit substances) during pregnancy and during the first 60 days postpartum. This study was approved by the University of Cincinnati Institutional Review Board.

2.3. Statistical analysis

We calculated descriptive statistics for all relevant variables. We divided subjects into higher dose (receiving an average daily dose of 60 mg methadone or more during pregnancy) and lower dose (receiving an average daily dose of<60 mg methadone during pregnancy) groups. We compared these 2 groups using Fisher's exact tests to compare treatment retention at delivery and at 60 days postpartum. Wilcoxon rank sum tests were used to compare percent of UDS results negative for illicit substances during pregnancy and during the 60-day postpartum period. Finally, we developed generalized linear models using treatment retention at delivery and at 60 days postpartum as the binary response variables. Predictors included maternal age, average daily methadone dose during pregnancy, length of time in treatment during pregnancy, and percent negative UDS results during pregnancy. Because previous studies of non-pregnant patients have shown a relationship between methadone dose and frequency of illicit drug use (Faggiano et al., 2003), we included an interaction term between methadone dose and percent negative UDS results.

3. Results

3.1. Sample characteristics

The characteristics of the subjects as a function of methadone dose (i.e., lower dose and higher dose groups) are provided in Table 1. There were 189 women included in this study with a mean age of 27.5 years (SD = 4.3, range 18–42). The population was almost exclusively non-Hispanic Caucasian (2.1% Hispanic ethnicity, 97.9% Caucasian race). The average daily methadone dose during pregnancy was 60.8 mg per day (SD = 22.9, range 10-150) with a median dose of 56 mg per day. The average number of days in treatment from identification of pregnancy to delivery or pre-delivery dropout was 128.6 (SD = 71.9, median 122, range 14–260). Participants completed a mean of 6.7 UDS tests during pregnancy (SD = 4.6, median 6, range 1–20) and a mean of 1.6 UDS tests in the first 60 days postpartum (SD = 1.4, median 2, range 0–6). Among women in the sample, 57.1% were in the lower dose group versus 42.9% in the higher dose group.

3.2. Retention in MAT-M

In the overall sample, 81.0% of subjects were retained in MAT-M antepartum (i.e., still enrolled in treatment at delivery) and 51.9% were retained in treatment for the 60-day postpartum period. As can be seen in Fig. 1, there were significant differences in both ante- and post-partum retention as a function of methadone dose. Treatment retention at delivery for higher dose subjects was 90.1% versus 74.1% for lower dose subjects (Fisher's exact test $p < 0.0053$). Treatment retention at 60 days postpartum was 71.6% for higher dose subjects versus 37.0% for lower dose subjects (Fisher's exact test $p < 0.0001$).

The results of the generalized linear models revealed significant methadone dose effects for both antepartum ($\chi^2 = 4.43$, $p < 0.02$) and postpartum ($\chi^2 = 8.5$, $p < 0.004$) treatment retention. Fig. 2 shows

Table 1
Participant characteristics and treatment profile as a function of methadone dose during pregnancy.

	Lower dose (<60 mg/day) (N = 108)	Higher dose (≥60 mg/day) (N = 81)	All participants (N = 189)
Age in years	27.0 (4.6)	28.1 (3.8)	27.5 (4.3)
Race/ethnicity, n (%)			
Caucasian	105 (97.2%)	80 (98.8%)	185 (97.9%)
African American	1 (1.0%)	0 (0%)	1 (0.5%)
Hispanic	2 (1.9%)	2 (2.5%)	4 (2.1%)
Other	2 (1.9%)	1 (1.2%)	3 (1.6%)
Daily methadone dose during pregnancy	45.9 (10.4)*	80.7 (19.6)*	60.8 (22.9)
Days in treatment during pregnancy[a]	97.4 (67.7)*	162.6 (64.2)*	128.6 (71.9)
Number of UDS during pregnancy	5.2 (4.1)*	8.7 (4.4)*	6.7 (4.6)
Number of UDS during 60 days postpartum	1.2 (1.3)*	2.1 (1.4)*	1.6 (1.4)

Note: Where not specifically indicated, numbers represent means (standard deviations). UDS = urine drug screen. * Groups differ significantly at $p < 0.001$ (Wilcoxon rank sum).
[a] Days in treatment from pregnancy identification to delivery or pre-delivery drop out.