Journal of Substance Abuse Treatment 47 (2014) 229–232

Contents lists available at ScienceDirect

Journal of Substance Abuse Treatment

Postpartum changes in methadone maintenance dose

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ARTICLE INFO

Article history:
Received 15 October 2013
Received in revised form 17 April 2014
Accepted 22 April 2014

Keywords:
Pregnancy
Postpartum
Opioid dependence
Methadone maintenance treatment

ABSTRACT

The optimal approach to postpartum dosing among women treated with methadone maintenance is unclear. We examined doses among 101 methadone-maintained pregnant women 2, 6 and 12 weeks postpartum, and compared the incidence of having doses held for oversedation during pregnancy and postpartum. The average dose at delivery was 83.3 mg, and the mean change from delivery to 12 weeks postpartum was −3.7 mg (95% CI −6.3, −1.1). The incidence of oversedation events per 10,000 days was 2.8 among pregnant women and 5.6 for postpartum women (incidence rate ratio [IRR] 2.04, 95% CI 0.66, 6.28). After adjusting for benzodiazepine prescriptions, the IRR of an oversedation event among postpartum women compared to pregnant women was 1.74 (95% CI 0.56, 5.30). In conclusion, postpartum dose changes were small in a methadone clinic using clinical assessments to determine dose. Although the incidence of oversedation events remained low postpartum, the clinically important but not statistically significant increase in events among postpartum women and those prescribed benzodiazepines requires further research. While there are not yet adequate data to support pre-specified postpartum dose reductions, the findings suggest that more frequent clinical assessments continuing as late as 12 weeks postpartum may be warranted.

1. Introduction

Among opioid dependent women who are pregnant, methadone maintenance treatment (MMT) reduces illicit opioid use, improves women's access to prenatal care, and improves neonatal outcomes, particularly birth weight (Bell & Harvey-Dodds, 2008; Jones, Martin, et al., 2008). Buprenorphine is used increasingly to treat opioid-dependent women who are pregnant, due to its availability in the office setting and evidence of decreased severity of neonatal abstinence syndrome (NAS) (Jones et al., 2010). Yet for many women, MMT continues to have advantages, including the structured treatment environment and methadone's properties as a full agonist with no ceiling effect, which may contribute to better retention in care (Jones et al., 2010).

Pregnancy offers powerful motivation for opioid dependent women to seek treatment, including MMT (Daley, Argeriou & McCarty, 1998). The postpartum period is thus a critical crossroads on the path to long-term recovery. Ensuring optimal methadone dosing during this period is important. Methadone doses must be sufficiently high, typically 60 mg or greater, to treat opioid withdrawal, reduce opioid cravings, and block opioid euphoria, all of which lead to reduced illicit opioid use and abstinence in both pregnant and non-pregnant opioid dependent populations (Faggiano, Vigna-Taglianti, Versino & Lemma, 2003; McCarthy, Leamon, Parr & Anania, 2005). Yet, the goal of providing an effective, sufficiently high dose needs to be balanced with concerns about the risks of oversedation.

Achieving this balance can be clinically complex, particularly in the postpartum period. Pregnant women often require increases in methadone dose throughout pregnancy due to factors such as increased intravascular volume, and increased tissue reservoir and hepatic metabolism of the drug (Center for Substance Abuse Treatment, 2005). The optimal approach to methadone dose management in the postpartum period, however, is not well-defined. Federal treatment guidelines state:

> "Current treatment practices include continuing methadone after delivery either at dosages similar to those before pregnancy or, for women who began methadone maintenance during pregnancy, at approximately half the dosages they received in the third trimester. However, no empirical data support these approaches, and any decrease should be based on signs of overmedication, withdrawal symptoms, or patient blood plasma levels." (Center for Substance Abuse Treatment [CSAT], 2005).

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http://dx.doi.org/10.1016/j.jsat.2014.04.004
0740-5472/

Prior observational studies found that women received minimal dose adjustments in the immediate period after delivery (Albright et al., 2011; Jones, Johnson, et al., 2008). Post-partum dose reductions to half the third trimester dose as described by CSAT in the quotation above were not described in these studies. However, only the smaller of these two investigations of women taking methadone ($n = 10$), reported on the incidence of overmedication among the women studied (Jones, Johnson, et al., 2008). In addition, these studies only followed women until 5 and 6 weeks postpartum, respectively. Hepatic methadone clearance may remain elevated until 6 weeks post-delivery, and it may take up to 12 weeks or more for intravascular volume and other hemodynamic parameters to return to pre-pregnancy status (Silversides & Colman, 2007; Tracy, Venkataramanan, Glover & Caritis, 2005). Thus, a longer post-delivery observation period of 12 weeks, with data on oversedation from a larger sample, would provide better guidance on dosing safety and effectiveness in this population (Jones, Johnson, et al., 2008). In the current study, we sought to describe dosing changes from delivery until 12 weeks postpartum among opioid dependent women in MMT, and to describe the rate of oversedation events in the postpartum period, compared to pregnancy.

2. Methods

2.1. Design

This study was a retrospective cohort study of women who initiated methadone maintenance while pregnant. The current analysis was part of a larger study whose aim was to compare substance use outcomes among pregnant and postpartum women receiving methadone as opioid agonist treatment.

2.2. Clinical context

Typically, pregnant women in this MMT program enrolled after an inpatient stay at an affiliated hospital, where they underwent an initial methadone titration. After the women were discharged and began outpatient MMT, the methadone providers, consisting of nursing staff and two supervising physicians, made further, more gradual dosing adjustments based on patients' clinical signs and symptoms. For example, women who reported ongoing cravings or withdrawal symptoms to providers or to their counselors were eligible for a dose increase, usually 5 mg, followed by an assessment at the window 4 days later, to ensure the adequacy and safety of the increase. The nurses used a template to assess signs of withdrawal or sedation/intoxication, including pulse, respiratory rate, pupil size, and blood pressure; they also evaluate symptoms such as rhinitis, diaphoresis, lacrimation, nausea/vomiting/diarrhea, gooseflesh and anxiety. In addition, they specifically asked about mid-day sedation when methadone levels typically peak. If the dose was changed again, another assessment took place 4 days later, and so on. Doses were decreased if women, their counselors, or a medical provider reported sedation, lethargy or other signs of possible overmedication. In addition, women who were observed to be oversedated at the dosing window had their dose for the day held, and the dose was subsequently re-evaluated. In such situations, MMT staff also attempted to contact, with the patient's permission, any other providers who were prescribing potentially sedating medications such as benzodiazepines to make them aware of the incident and to coordinate care.

After delivery, women had a nursing assessment on the day of their return to the clinic, when in addition to doing a clinical assessment, the nurse confirmed the woman's hospital methadone dose by telephone with the inpatient nursing staff. Any dose changes made at that visit were typically discussed with the physician by phone, and were followed by assessments following the same protocol as during the pregnant phase. In addition, a methadone physician assessment was scheduled within 2 weeks postpartum.

2.3. Subjects

Women who enrolled in the methadone clinic between February 1, 2006, and January 31, 2010 were eligible for this study if they were pregnant at enrollment. Of note, because of the aims of the larger study, we excluded from data collection all women who miscarried or terminated their pregnancies, or who had two consecutive pregnancies within 18 months of their initial enrollment in the clinic. For the purposes of the current analysis of methadone dose changes, we further excluded women who left MMT before 12 weeks after delivery.

2.4. Data collection

We reviewed the electronic medical records of the methadone clinic and the affiliated medical center. The two main outcomes examined were daily methadone dose received and the number of days when women had doses held for oversedation (i.e. oversedation events). Other data included patient demographics, health-related characteristics (i.e., HIV status, receipt of benzodiazepine prescriptions during pregnancy and postpartum, and smoking at enrollment) and MMT-related factors (i.e., previous MMT and take home privileges). Of note, although usually the term postpartum is used for women who have delivered within the last 6 weeks, we have used the term "postpartum" to refer to women up to 12 weeks after delivery.

2.5. Analysis

For demographic and health-related characteristics of the sample, we generated descriptive statistics, including frequencies for categorical variables, and means, medians and standard deviations for continuous variables. In addition, we calculated the mean methadone dose received at delivery, and the mean weekly dose received postpartum. We calculated the mean change in dose between delivery and 2, 6 and 12 weeks postpartum and used paired t-tests to determine whether the differences between methadone doses were statistically significant. Using generalized estimating equations (GEE) Poisson regression, we calculated the incidence rate ratio and associated 95% confidence interval (CI) for oversedation events among postpartum compared to pregnant women across time. Because benzodiazepines were considered to be an important potential confounder, we then calculated an incidence rate ratio and 95% CI for oversedation events among postpartum compared to pregnant women, controlling for benzodiazepine prescriptions. We also calculated an incidence rate ratio and 95% CI comparing women prescribed benzodiazepines to women not prescribed benzodiazepines. The models included an offset for the total number of dosing days in a given time period to account for unequal observation times. All data analyses were generated using SAS/STAT software, version 9.3 of the SAS System for Windows (SAS Institute, Inc., 2002–2010). Statistical significance was two-tailed and defined as $p < 0.05$.

2.6. Human subjects protections

Approval for this study was obtained from the Boston University Medical Campus Institutional Review Board, which represents both the medical center and the MMT program. Because this was a retrospective medical record review in which no identifying information was collected, the requirement for informed consent was waived.