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Maternal methadone dosing schedule and fetal neurobehavior

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Abstract

Objective—Daily methadone maintenance is the standard of care for opiate dependency during pregnancy. Previous research has indicated that single-dose maternal methadone administration significantly suppresses fetal neurobehaviors. The purpose of this study was to determine if split-dosing would have less impact on fetal neurobehavior than single-dose administration.

Methods—Forty methadone-maintained women were evaluated at peak and trough maternal methadone levels on single- and split-dosing schedules. Monitoring sessions occurred at 36 and 37 weeks gestation in a counterbalanced study design. Fetal measures included heart rate, variability, accelerations, motor activity and fetal movement-heart rate coupling (FM-FHR). Maternal measures included heart period, variability, skin conductance, respiration and vagal tone. Repeated measure analysis of variance was used to evaluate within-subject changes between split- and single-dosing regimens.

Results—All fetal neurobehavioral parameters were suppressed by maternal methadone administration, regardless of dosing regimen. Fetal parameters at peak were significantly lower during single vs. split methadone administration. FM-FHR coupling was less suppressed from trough to peak during split-dosing vs. single-dosing. Maternal physiologic parameters were generally unaffected by dosing condition.

Conclusion—Split-dosed fetuses displayed less neurobehavioral suppression from trough to peak maternal methadone levels as compared to single-dosed fetuses. Split-dosing may be beneficial for methadone-maintained pregnant women.

Keywords

methadone; methadone dosing; pregnancy; fetus; fetal neurobehavior

Introduction

Methadone is currently the standard of care for opiate dependence during pregnancy in the U.S., and its use has been demonstrated to yield multiple beneficial effects for this high risk and vulnerable population (1). This medication is typically delivered once daily due to a long half life. In non-pregnant patients, the half life of methadone is approximately 22 hours (2), but methadone pharmacokinetics are altered during pregnancy; methadone elimination is more rapid (3), and clearance rates increase over the course of pregnancy (4), leading some

investigators to conclude that split dosing may be beneficial during late gestation to maintain steady-state maintenance (3,5,6). There have been few empirical reports on this topic. In one, split dosing in pregnant women was associated with improved urine toxicology compliance rates and fewer positive urine toxicologies in the third trimester when compared to women receiving single dosing (7). A case report of a late twin gestation examined serial plasma methadone concentrations in a mother reporting withdrawal symptoms 10-12 hours after a small, single daily oral dose (30 mg). A pharmacokinetic model was employed to estimate a reduced methadone half life of 8.1 hours. Extrapolating the data to 24 hours, the authors postulated that splitting the total dose into two doses 12 hours apart would result in more sustained maternal plasma methadone levels than an increased dose, fewer maternal withdrawal symptoms in the mother and infant, and improved compliance with drug treatment (8).

It has been demonstrated that fetal neurobehaviors are affected by single dose methadone administration. In a study using an electronic fetal monitor equipped with fetal motor activity detection, it was found that fetal heart rate was slower and less variable, fetuses displayed less motor activity, and the coupling between movement and heart rate was attenuated at the time of peak maternal methadone levels as compared to trough levels (9). Another study, relying on ultrasound-visualized behaviors, found decreased fetal breathing and body movements during peak maternal methadone levels in women on single dose methadone therapy, regardless of dose, as compared to both the same fetuses at times of trough maternal methadone levels and to non-opioid dependent controls; the latter two groups being without significant differences. This author concluded that splitting the daily methadone dose might be detrimental to the fetus due to the depression of fetal activity after each methadone dose regardless of daily prescribed dose (10). The potential beneficial implications of split dosing for the fetus are generally accepted (11), yet there is only one study to examine the effects on the fetus under split and single dosing conditions. In it, seven methadone maintained women at 26 to 37 weeks gestation were evaluated via paired ultrasound examinations at times of trough and peak maternal methadone levels on single dose methadone therapy, followed by similar examinations during split (i.e. every 12 hours) dose methadone therapy later during an unspecified gestational period. Significant reduction in fetal body movements and fetal breathing activity and an increase in the longest period of fetal inactivity were noted during single dose exposure. A similar but non-significant trend was noted at times of trough vs. peak maternal methadone levels on a split dose regimen. The results of single dosed fetuses differed significantly from non-addicted controls matched for gestational age; the results of split dosed fetuses were similar to controls. The author concludes that split methadone dosing should be offered to pregnant opiate dependent women on methadone therapy when single dose treatment produces maternal withdrawal symptoms or abnormal fetal activity patterns (12).

The purpose of the current study was to determine if split methadone dosing would have less impact on fetal neurobehavior than single dose administration on a larger sample of participants and controlling for gestational age. To evaluate this, fetuses were monitored during single and split methadone dosing therapy, counterbalancing for gestational age at each regimen. We hypothesized that split-dosed fetuses would display less profound suppression of fetal neurobehaviors than single-dosed fetuses. In addition, continuous maternal physiologic data were collected to examine whether maternal autonomic measures were differently affected by dosing regimen.

Methods

Participants

Forty-two methadone maintained women, meeting DSM IV-R criteria for opiate dependence and federal guidelines for methadone maintenance, were selected from a population of women

engaged in substance abuse treatment at an urban, multidisciplinary, comprehensive care substance abuse treatment program (13) for pregnant and postpartum substance abusing women and their children. Participants were selected based on abstinence from illicit drug use and licit drug abuse (including alcohol, not including nicotine) after 28 weeks of gestation and compliance with program standards. To minimize confounds based on pregnancy risk factors, inclusion was limited to women with uncomplicated singleton pregnancies, who were HIV negative, and free of significant pregnancy complications, such as hypertension and gestational diabetes. Women with any concurrent diagnosis of alcohol dependence were excluded from enrollment. The research was approved by the governing institutional review board and informed consent was obtained from all participants.

Participants were enrolled at 32 weeks gestation. Estimation of gestational age was based on a sonogram performed between 16 and 20 weeks gestation in all cases, and was confirmed by postnatal assessment. Participants were disenrolled for any evidence (urine toxicology testing, performed minimally once per week, or clinically appearing intoxicated/altered) of drug or alcohol use.

One participant was disenrolled from further testing due to relapse to drug use after the first session. Another underwent testing, and it was later discovered that her methadone dose had been increased at her request between the two (single and split) fetal testing sessions; her data were discarded, leaving a total sample of 40 subjects.

Procedure

Data collection involved four 60-minute fetal monitoring sessions for each subject. The first two sessions occurred at times of trough maternal methadone level (one hour prior to morning oral methadone dose) and peak (2.5 hours after morning methadone dose) during the 36th week, and the second two at times of trough and peak maternal methadone levels during the 37th week of gestation. For half ($n=20$) of the subjects, the first monitoring session at 36 weeks gestation was performed on a single dose, and the other half were initially monitored at 36 weeks gestation on a split dose. The determination of first session on a split vs. single dose was made via a random numbers table.

Single dosing was delivered at 10:00 and observed; split doses were delivered and observed at 10:00, and taken at home, unobserved, at 22:00. Participants had their total dose split into two equal doses, taken 12 hours apart, one week before the split dose session. Peak plasma methadone levels in individuals chronically treated with oral methadone occur between 2 to 4 hours after an oral daily dose (14). The dose of methadone did not change between the split and single monitoring sessions (M dose = 72.9 mg, SD 19.6; range 20 to 120 mg). Other medications, including psychotropic drugs, did not change in type, dose or amount between sessions.

In both conditions, the trough methadone monitoring session occurred prior to administration of the 10:00 methadone dose. The peak methadone monitoring session occurred at 13:30, or 2.5 hours after the administration of the dose. Women were asked to eat a meal and refrain from caffeine and/or cigarettes 2 hours prior to each session in an effort to control for maternal glycemic status and the effects of caffeine and nicotine on the fetus. Recent cigarette smoking was evaluated at both sessions by breathalyzer testing for CO using the Micro Smokerlyser (Bedfont Scientific Limited; Kent, UK). Carbon monoxide levels in parts per million were recorded; values were not adjusted for background levels. Recent alcohol use was similarly evaluated using a Digitox-D.O.T. (Sound Off, Inc., Hudsonville, MI) screening breath tester, which measures blood alcohol content to 0.02 %, or the equivalent of one drink. Urine was obtained for toxicology at both sessions. Participants' perceived symptomatology indicative of

opiate withdrawal was surveyed at each test session using the Subjective Opiate Withdrawal Scale (SOWS) (15).

Primary Outcome Measures

Fetal Neurobehavioral Assessment—Fetal data were collected using a Toitu (MT325) fetal actocardiograph. This monitor detects fetal movement (FM) and fetal heart rate (FHR) using a single wide array transabdominal Doppler transducer and processes this signal through a series of filters. The actograph detects fetal movements by preserving the remaining signal after bandpassing frequency components of the Doppler signal that are associated with FHR and maternal somatic activity. Reliability studies comparing actograph based versus ultrasound visualized fetal movements have found the performance of this monitor to be highly accurate in detecting both fetal motor activity and quiescence (16). Fetal data were collected from the output port of the monitor and digitized at 1000 Hz through an internal A/D board using streaming software. Data were analyzed off-line using customized software (James Long Company, Caroga Lake NY). Digitized heart rate data underwent error rejection procedures based on moving averages of acceptable values as needed. Four fetal cardiac variables were extracted: fetal heart rate and variability (root mean squared) computed for each 1-min epoch averaged over time, and accelerations and decelerations. Accelerations were identified when FHR values attained 10 bpm above baseline for greater than or equal to 15 sec; decelerations defined as ≤ 15 bpm below baseline for greater than or equal to 15 sec.

Fetal movement measures were based on the actograph signal, which ranges from 0 to 100 in arbitrary units. Average motor activity was also calculated for 1 minute epochs and the mean these epochs was used to quantify average motor activity for each 60 minute session. FM-FHR coupling was calculated as the percentage of fetal movements associated with excursions in $FHR \geq 5$ bpm over baseline within 5 sec before the start of a movement or within 15 sec after the start of a movement.

Maternal Physiologic Assessment—Maternal physiological signals were amplified using a multi-channel, electrically isolated bioamplifier. Electrocardiogram (ECG) was recorded from 3 carbon fiber disposable electrodes in triangulated placement (right mid sub-clavicle, left mid axillary thorax, and upper left thigh for ground lead). Electrodermal activity (i.e., skin conductance) was monitored from two silver-silver chloride electrodes with a gelled skin contact area placed on the distal phalanges of the index and second fingers of the non-dominant hand affixed with adhesive collars to limit gel contact to a 1 cm diameter circle, and velcro.

Maternal data were time synchronized and analyzed in conjunction with fetal data. ECG data underwent R-wave detection, manual editing for artifact, and interbeat interval computation. Skin conductance was measured by administering a constant 0.5 volt root-mean-square 30 Hz AC excitation signal and detecting the current flow. Skin conductance was scaled from 0 to 25 microsiemens and detrended to remove the mean, thereby amplifying the signal to noise ratio (-2.5 to +2.5 microsiemens). Maternal ECG values were quantified as heart period (i.e., interval between R-waves in msec), and heart period variability (standard deviation of successive heart periods). Digitized ECG data were processed using the IBI Analysis System (James Long Company, Caroga, NY). R-waves were automatically extracted using a pattern matching algorithm and manually verified and edited by visual inspection of the raw ECG. Vagal tone computation followed a strategy similar to that developed by Porges (17). Interbeat interval data were detrended to remove tonic shifts over time. The residual, detrended data were spectrally analyzed by Discrete Fourier Transform for the frequency band associated with spontaneous respiration (.12 to .40 Hz) and the resultant variance, after undergoing a natural

logarithm transformation, serves as the estimate of the magnitude of the respiratory sinus arrhythmia, or vagal tone. Maternal variables were averaged during the recording.

Analysis

Variables were examined for outliers more than 3 *SD* from the mean and skewness. A series of 2×2 repeated measures analysis of variance (RMANOVA) were used to evaluate the effects of dosing condition (single vs. split dose) and change from trough to peak maternal methadone levels on fetal neurobehavioral function and maternal physiology. Correlational analysis was used to examine associations between methadone dosage, use of other substances (i.e., cigarettes, psychotropic medications), and change in fetal and maternal measures from trough to peak. Percent change scores were calculated to reflect the magnitude of change in maternal and fetal measures from trough to peak using the following formula: $((\text{peak} - \text{trough})/\text{trough}) \times 100$. Higher scores indicate an increase from trough to peak, while lower scores indicate a decline.

Results

Participants tended to be multigravid (80%), near 30 years of age ($M = 28.1$ years, $SD = 5.4$), and Caucasian (70%; 25% African American, 2.5% Biracial, 2.5% Hispanic). Eleven participants (27.5%) took prescribed psychotropic drugs: fluoxetine (5) and sertraline (3), and bupropion (3). Three required antibiotics (7.5%) and 3 antiemetics (7.5%). One subject (2.5%) each required asthma medications and synthetic thyroid hormone (this subject was closely monitored and remained euthyroid throughout her pregnancy, so was retained in the final sample). Most (87.5%) smoked cigarettes regularly; the mean number of cigarettes smoked daily was 11.7 ($SD = 6.57$, range = 3-30). No subject reported significant withdrawal symptoms using the SOWS questionnaire. Most women reported a preference for single methadone dosing (65%); 32.5% preferred split dosing. Additional information on maternal characteristics and drug history is presented in Table 1.

Women appeared to be compliant with the request to refrain from smoking and alcohol consumption prior to each visit. No appreciable levels of alcohol were detected via alcohol screening by breathalyzer for any subject at the time of fetal testing. Carbon monoxide levels were not different between trough ($M = 7.45$, $SD = 5.60$) and peak ($M = 8.33$, $SD = 5.33$), $t(39) = 1.38$, *ns*.

Twelve of the fetuses were male (30%) and all were born at term (>37 weeks gestation). Birth weights were appropriate for gestational age (see Table 2). There was no evidence of intrauterine growth retardation for any infant. All 5-minute Apgar scores were ≥ 7 . Infants were without significant neonatal morbidity aside from Neonatal Abstinence Syndrome, which occurred with pharmacologically treatable significance in 27 (67.5 %).

Effect of Methadone Dosing on Fetal Neurobehavior

Descriptive statistics and results for fetal neurobehavioral measures are presented in Table 3. Decelerations in heart rate were too uncommon (present in 4 fetuses during single trough and split peak sessions and 6 fetuses during single peak and split trough sessions) to be analyzed. In the single condition, 2 cases were missing at trough for fetal motor activity and FM-FHR coupling due to artifact generated by heavy fetal breathing motions. In the split condition, 1 case was missing for all fetal variables at trough due to technical difficulties with instrumentation. Fetal heart rate, heart rate variability, the number of fetal heart rate accelerations, and FM-FHR coupling declined from trough to peak methadone levels. There was a trend reduction in fetal motor activity. Significant changes between peak and trough were observed in both the split and single dosing conditions. With respect to the use of split

or single dosing, main effects for dosing condition were observed for fetal heart rate, heart rate variability and motor activity. Planned contrasts revealed each fetal neurobehavior value was higher at peak during the split condition as compared to peak levels during single dosing (FHR: $t(39) = 3.01, p < .01$; FHRV: $t(39) = 2.27, p < .05$; FM: $t(39) = 3.56, p < .01$). The suppressive effects of single dosing were similar in direction for fetal heart rate accelerations, but did not attain significance, $F(1,37) = 2.08, p = .16$. When examining FM-FHR coupling, a significant dose by time interaction emerged, $F(1, 36) = 7.73, p < .01, \eta = .18$, such that FM-FHR coupling declined in both conditions from trough to peak maternal methadone levels, but the reduction was greater during the single (M change = -35.9%) as compared to the split dose condition (M change = -8.5%), $t(35) = 2.79, p < .01$. This finding is presented in Figure 1.

Effect of Methadone Dosing on Maternal Physiological Measures

Descriptive statistics for maternal physiological measures are presented in Table 4. Three maternal heart rate variability outliers due to movement artifact were removed; 2 at peak in the single dose condition and 1 at trough in the split condition. One case was missing at trough in the split condition due to technical difficulties with recording.

Few maternal physiological measures were influenced by methadone administration. Maternal skin conductance declined significantly from trough to peak methadone level during both single and split conditions; however this finding is tempered by a significant interaction for this measure such that the decline in maternal skin conductance was greater during the split condition ($M = -1.82$ microsiemens) as compared to the single condition (-0.85 microsiemens, $t(38) = 2.04, p < .05$). There was a main effect of dosing only for maternal heart rate variability, which was significantly higher at peak during the single ($M = .053$) as opposed to the split condition ($M = .047$), $t(37) = 2.70, p < .05$.

Methadone Dosage

Methadone doses ranged from 20 to 120 mg daily and number of days on treatment ranged from 51 to 258 days. Potential relations between the degree of change from trough to peak for fetal and maternal measures with methadone dose and treatment length were examined. Partial correlations, controlling for trough levels, were computed between each fetal and maternal measure with dose and treatment duration. No significant associations with methadone dose or treatment duration were detected in the single dose condition. In the split condition only, more total days in treatment was associated with less decline in fetal heart rate variability from trough to peak, $r(36) = .32, p = .05$, and with a greater decline in maternal heart rate variability, $r(36) = -.39, p < .05$.

Discussion

Decisions concerning methadone dose scheduling during pregnancy are difficult due to sparse research and unclear guidelines in this arena. While it has been established that the pharmacokinetics of methadone metabolism change during gestation, guidelines for optimal dosing in pregnant women are not established and rely primarily on subjective patient report. In the current study, which evaluated the same women on both single and split dosing, maternal methadone administration, irrespective of dosing schedule, was associated with suppression in fetal heart rate, variability, accelerations, motor activity, and FM-FHR coupling. These findings replicate those reported for single dose administration only (9). However, during the fetal testing sessions in which women were receiving split dose administration, less overall suppression of fetal neurobehaviors were evident. That is, at the times of peak maternal methadone levels during split dosing, fetal heart rate, variability, and motor activity were higher than those at the times of peak levels during single dosing. The synthetic measure of FM-FHR coupling displayed a slightly different response pattern than single measures of cardiac or

motor functioning. The degree of decline observed between trough and peak sessions for single dosed fetuses was significantly more pronounced than the decline between trough and peak sessions for split dosed fetuses, during which minimal change was evident. FM-FHR coupling has been implicated as a particularly useful measure of autonomic control during pregnancy (18,19). It has been demonstrated that behavioral alterations in methadone exposed neonates may be related to impaired autonomic or parasympathetic functioning (20), therefore, this fetal parameter may be most likely to manifest changes due to maternal methadone administration.

This evaluation of single vs. split dosing in late gestation has demonstrated that methadone therapy in either form impacts fetal neurobehaviors, and that split dosing lessens, but does not completely ameliorate, the effects of methadone on fetal neurobehavior. The observation of changes in fetal behaviors in the absence of significant maternal physiological changes or perceived withdrawal symptomatology, suggests that these changes are specific to direct effects of methadone on the fetus. In addition, despite the wide range in methadone doses, the lack of significant associations between maternal dose and either maternal or fetal measures is consistent with previous reports of a lack of association of methadone dose and plasma levels in pregnant women (21), lack of association between maternal methadone dose and plasma concentrations of methadone in the neonate (22), as well as the generally accepted lack of association between maternal methadone dose and severity of neonatal abstinence syndrome in the exposed neonate (20,23).

The results indicate that split dosing might be a preferable strategy for pregnant women maintained on methadone because it reduces fetal neurobehavioral effects without significantly altering maternal physiological indicators. However, it should be noted that the population studied was abstinent from illicit drug and alcohol use from 28 weeks until delivery and treatment program compliant, allowing the distribution of methadone as a take home dose, thereby potentially introducing a selection bias that may affect generalizability to the general population. Moreover, this strategy may not apply for all pregnant methadone maintained women or programs treating them, as ideal split dosing is every 12 hours requiring take home medication dosing, which is generally offered to more stable treatment participants who are unlikely to abuse or sell the take home dose. However, the concept that split dosing affects fetal neurobehaviors in a less profound way than single dosing in late gestation can be used to establish guidelines for some opiate dependent pregnant women who require methadone. When asked their preference for methadone dosing schedule, most subjects (65%) reported preferring a single to a split methadone dose during their pregnancy. However, nearly all (37, or 92.5%) reported that they would agree to split dosing if they were informed that it was optimal for their infant.

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Figure 1.

Decline in fetal movement-fetal heart rate coupling was significantly greater in the single as compared to the split methadone dosing condition.

Table 1

Maternal drug use and methadone maintenance (n=40).

	Mean (sd)
Age at first drug use (years)	16.5 (4.3)
Age at time of regular (3×/week or more) drug use (years)	19.7 (3.8)
Years of regular drug use	7.7 (4.7)
Age at current pregnancy (years)	28.1 (5.4)
Methadone dose (mg)	72.9 (19.6)
Length of time in drug treatment at testing (days)	166.3 (45.9)
Initiation of methadone maintenance	
Preconception	7(17.5%)
First trimester	13 (32.5%)
Second trimester	19 (47.5%)
Third trimester	1 (2.5%)

Table 2

Perinatal parameters (n=40).

	Mean (sd)
Birth weight (g)	3216.0 (564.3)
Birth length (cm)	50.0 (3.1)
Birth head circumference (cm)	33.6 (1.5)
Gestational age at delivery (weeks)	39.5 (1.2)
Apgar at 1 minute	8.1(1.5)
Apgar at 5 minutes	8.9(0.6)

Table 3
Fetal neurobehavioral measure by time and methadone dosing condition ($n = 40$).

	Single Dose		Split Dose		Time: Trough to Peak		Dose: Split vs. Single		Time $\times$ Dose	
	Trough Mean (SD)	Peak Mean (SD)	Trough Mean (SD)	Peak Mean (SD)	F		F		F	
Heart rate (bpm) ^a	138.26 (8.56)	130.39 (8.75)	139.50 (9.98)	133.39 (1.29)	63.11***		6.60*		1.15	
Heart rate variability ^a	5.93 (1.51)	4.11 (1.51)	6.27 (2.14)	4.58 (1.29)	61.60***		11.16**		.22	
Accelerations ^b	3.60 (3.24)	1.10 (1.88)	4.08 (4.09)	1.28 (1.82)	36.22***		2.08		.18	
Motor activity ^b	5.74 (2.12)	4.62 (1.41)	6.07 (2.38)	5.64 (2.21)	3.56		8.21**		.83	
FM-FHR Coupling ^c	.23 (0.09)	.13 (0.09)	.22 (0.09)	.17 (.10)	23.55***		1.95		7.73**	

*
p<.05,

**
p<.01,

p<.001

^aDegrees of freedom = (1, 38)

^bDegrees of freedom = (1, 37)

^cDegrees of freedom = (1, 36)

Table 4
Maternal physiological measures by methadone dosing condition ($n = 40$).

	Single Dose		Split Dose		Time: Trough to Peak	Dose: Split vs. Single		Time $\times$ Dose
	Trough Mean (SD)	Peak Mean (SD)	Trough Mean (SD)	Peak Mean (SD)		F	F	
Heart rate (bpm) ^a	82.28 (13.69)	82.09 (11.48)	83.07 (13.32)	82.23 (11.78)	.48	.25		1.05
Heart rate variability ^b	.051 (0.021)	.053 (0.023)	.053 (0.023)	.048 (0.020)	.04	4.57*		2.06
Vagal tone ^a	4.14 (2.87)	3.64 (2.31)	3.64 (2.31)	3.92 (2.51)	.01	.00		1.20
Skin conductance ^a	4.20 (4.21)	3.44 (4.45)	4.75 (4.43)	2.84 (3.10)	16.31***	.01		4.18*

* $p < .05$,

** $p < .01$,

*** $p < .001$

^a Degrees of freedom = (1, 38)

^b Degrees of freedom = (1, 35)