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Pregnancies exposed to methadone, methadone and other illicit substances, and poly-drugs without methadone: A comparison of fetal neurobehaviors and infant outcomes

L.M. Jansson¹, J.A. Di Pietro², A. Elko³, E.L. Williams², L. Milio³, and M. Velez¹

¹Johns Hopkins University School of Medicine, Department of Pediatrics, Baltimore MD 21224, USA

²Johns Hopkins Bloomberg School of Public Health, Department of Population, Family and Reproductive Health, Baltimore, MD 21205, USA

³Johns Hopkins University School of Medicine, Department of Obstetrics and Gynecology, Baltimore, MD 21224, USA

Abstract

BACKGROUND—It is suspected that there is a continuum of impairment among prenatally drug-exposed infants, such that opioid and/or poly-drug exposure confers the highest risk for adverse neonatal outcomes than other classes of substances or single substance exposures. Suitable control groups are difficult to identify. This study compared fetal neurobehavioral development and infant outcomes in offspring of three groups of pregnant women in drug treatment. Exposure groups include: Methadone + other illicit substances (MM+Poly) and two groups currently abstinent for poly drug exposures: Methadone only (MM/A) and Non-methadone (NM/A).

METHODS—Forty-nine women (19 MM+Poly, 18 MM/A, and 12 NM/A) underwent fetal monitoring at 36 weeks gestation at peak and trough levels of methadone (MM+Poly; MM/A) or at comparable morning and afternoon times (NM/A). Fetal heart rate (FHR), heart rate variability (FHRV) and motor activity (FM) data were collected. Infant measures included birth outcomes and Neonatal Abstinence Syndrome (NAS) assessment.

RESULTS—As compared to the NM/A group, cardiac measures were decreased in methadone-exposed fetuses at peak levels. FHR was significantly more suppressed in the MM+Poly group. FM was significantly lower in the MM/A versus the NM/A group at both peak and trough, indicative of more persistent exposure effects. The MM+Poly group delivered one week earlier and required NAS pharmacological treatment twice as often as the MM/A group.

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Corresponding author: Lauren M. Jansson, Johns Hopkins University School of Medicine, 5200 Eastern Avenue, D5, Baltimore, MD 21224, Phone: 410-550-5438, Fax: 410-550-2713, ljansson@jhmi.edu.

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CONCLUSIONS—Results support the notion that poly-drug exposure may potentiate the effects of methadone on the fetus and infant and highlights the need for intensified treatment for methadone-maintained women who abuse other substances.

Keywords

Poly-drug exposure; fetal neurobehavior; neonatal abstinence syndrome; methadone

1. INTRODUCTION

Drug use during pregnancy continues to be a public health concern internationally, but there remains a relative dearth of information regarding the effects of maternal drug use on the developing fetus with its implications for infant functioning. Neonatal dysfunction may be dependent on a host of maternal, fetal and infant factors in addition to the direct toxic effects of illicit drug exposure. These may include genetic vulnerability, epigenetic variation and fetal programming (Salisbury et al., 2009), maternal and infant autonomic functioning (Jansson et al., 2007; Jansson et al., 2010), maternal psychopathology (Tuten et al., 2009), licit exposures including cigarettes (Stroud et al., 2009; Law et al., 2003), alcohol (Cotes et al., 1985) and psychotropic medications (Rampono et al., 2009), maternal stress (Vrekoussis et al., 2010), and socioeconomic class (DiPietro et al., 1998). These factors likely interact in a unique manner within each individual pregnancy and are difficult to identify and quantify. A nearly constant criticism of the extant literature on drug-exposed infants is the failure to include an appropriate control group. Yet, due to the multiple social and biologic confounders inherent in a population of drug-dependent pregnant women, identifying an appropriate control group is difficult. Studies that include only a non-exposed comparison group fail to adequately account for the potential non-drug influences on outcomes that are inherent in the addicted woman's life.

Methadone introduces a unique confound in research on the effects of maternal opioid dependence. While it is clear that methadone maintenance confers significant maternal benefit (Jones et al., 1999), the methadone-exposed fetus shows a number of alterations in neurobehavioral functioning suggestive of lack of well-being. When compared to non-drug exposed controls, methadone-exposed fetuses show diminished reactivity in non-stress testing (Archie et al., 1989; Anyaegbunam et al., 1997; Levine and Rebarber, 1995; Cejtin et al., 1996) and reduced fetal breathing and fetal motor activity (Wouldes et al., 2004) shortly after methadone dosing. Methadone-exposed fetuses exhibit slower and less variable heart rates, fewer heart rate accelerations, less motor activity and attenuated integration between heart rate and motor activity (Jansson et al., 2005). Such measures of fetal neurobehavioral functioning reveal information about the developing fetal nervous system (DiPietro et al., 2001), and predict newborn neurobehaviors (DiPietro et al., 2010), which are associated with medical and behavioral outcomes (Liu et al., 2009; Lester et al., 2009) and as such, indicate the possibility of long term impairment as a result of prenatal methadone exposure. The methadone-exposed infant is at significant risk for NAS (Finnegan, 1991) and displays altered neurobehavioral performance after delivery (Velez et al., 2009). However, studies controlling for sociodemographic, biologic and health factors have generally found no differences in development among methadone- vs. non-exposed controls (Lifschitz et al., 1985; Kaltenbach and Finnegan, 1989).

Despite the accumulating body of evidence that methadone affects neurodevelopmental functioning in the fetus and infant, the effects of maternal poly-drug use in addition to, or in the absence of methadone are generally unknown. The multiple risk model associates the likelihood of infant morbidity with the number of maternal risk factors; maternal chemical use represents one such factor (Gustavsson, 1992). According to this model, there is a

continuum of impairment in drug-exposed neonates such that infants exposed to multiple substances have poorer neonatal outcomes than infants exposed to single drugs, with opioid-exposed infants, as a result of their propensity to display significant NAS, having the poorest outcomes overall. Despite the fact that poly-drug use is more common than single-drug use, there is scant information on poly-drug effects on the infant (Lester et al., 2004). One large prospective longitudinal study found that effects of multiple drugs can be detected even at low thresholds in poly-drug exposed 1-month-old infants using neurobehavioral tests that are differentially sensitive to drug effects (Lester et al., 2002). In addition, opioid-exposed infants have been found to have poorer state control and reduced interactive behaviors than multiple-drug, non-opioid-exposed infants, who in turn have poorer neurobehavioral outcomes than non-drug-exposed control infants (Chasnoff et al., 1982). Therefore, a useful set of comparisons would be to compare a group of opioid-dependent women who abstained from other illicit drugs during methadone maintenance, opioid-dependent women who received methadone but continued to abuse other illicit substances, and women who used illicit substances during early gestation but did not receive methadone maintenance.

This study compared fetal neurobehaviors and neonatal outcomes among three such groups. We hypothesized that there would be a continuum of effects indicative of fetal neurological development such that non-methadone, other drug abstinent group fetuses would have the most mature patterns of fetal neurobehavioral functioning, followed by methadone only-exposed fetuses, who in turn would display indicators of more optimal neurobehavioral functioning than those fetuses exposed to both methadone plus poly-drugs. We additionally hypothesized that early infant functioning would parallel the fetal findings, with methadone and poly-drug exposed infants exhibiting more Neonatal Abstinence Syndrome (NAS) symptomatology, which is a reflection of dysregulation neurobehavioral functioning.

2.METHODS

2.1 Participants

Participants were pregnant women enrolled in a comprehensive urban drug treatment center that treats pregnant and post-partum women and their children. The program is described elsewhere (Jansson et al., 1996). Inclusion criteria included singleton pregnancies with normal fetal growth and absence of anomalies as identified by an obstetrical sonogram and negative serum quad screening. For women receiving methadone maintenance, inclusion criteria also included single daily dosing, as split as compared to single methadone dosing has been shown to differentially affect fetal neurobehaviors (Jansson et al., 2009a). Exclusion criteria based on maternal conditions which may independently affect fetal development included medical conditions (e.g., HIV+ status, maternal syphilis, hypertension, Type 1 or gestational diabetes) and diagnosed alcohol dependency per DSMIV-R criteria. Also excluded were women with significant psychopathology that would preclude informed consent as identified by psychiatric examination. Women were screened at 28 weeks gestation and enrolled in the study shortly thereafter. Enrollment occurred between May 2006 and May 2009. The study was approved by the governing institutional review board; all participants provided written, informed consent.

All participants had random urine toxicology screening at least once per week as per standards of the treatment facility for the following: amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, opiates, phencyclidine, methadone, propoxyphene and alcohol. Examination of maternal records at 35 weeks gestation determined participant assignment into one of three groups based on parameters defined below.

Group I: Opioid-dependent, methadone-maintained and poly-drug using women (MM+Poly group; n = 18)—Participants included opioid-dependent,

methadone-maintained women on a stable methadone dose between 35 and 36 weeks of gestation who had at least one urine toxicology screening after 32 weeks of gestation that was positive for one or more substances excluding methadone (indicating illicit drug use or licit drug misuse). Urine drug screens were presumed positive if the participant failed to leave a urine specimen for analysis, or if the urine was methadone-negative for women on methadone maintenance, indicating misappropriation of urine for toxicology screening, or “rigging.” There were no requirements for a period of drug abstinence or treatment compliance prior to 36 weeks of gestation, aside from presenting on the day of fetal testing with a negative urine toxicology screening. This group contained a variety of overlapping drug using conditions per urine toxicology after 32 weeks of gestation, including benzodiazepines (5), barbiturates (1), cocaine (6), THC (1), non-methadone opioids (6), and methadone-negative (7).

Group II: Opioid-dependent, methadone-maintained and currently drug-abstinent women (MM/A group; n = 19)—Participants were opioid-dependent, methadone-maintained and abstinent from illicit drug use and licit drug misuse after 32 weeks gestation (i.e., no positive excluding methadone or methadone-negative urine screening). They were on a stable dose of methadone between 35 and 36 weeks of gestation, had good program compliance and no positive urine toxicology screenings between 32 and 36 weeks of gestation.

Group III: Non-methadone maintained and currently drug-abstinent women (NM/A group; n = 12)—Participants included women reporting any gestational drug use but had no period of methadone maintenance during gestation. Participants in this group remained affiliated with the treatment program but either opted out of or did not meet criteria for methadone maintenance. This group includes a variety of overlapping drug using conditions *prior* to 32 weeks gestation, including opioids (7), cocaine (5), THC (3), alcohol (3) and benzodiazepine misuse (1), but abstinence from illicit drug use and licit drug misuse (i.e., no positive urine screening including methadone), and treatment compliant *after* 32 weeks of gestation, including at the time of testing. Three non-methadone-maintained, poly-drug users tested positive after 32 weeks gestation and as such did not fit into any group assignment and so are not included in the analyses.

The period of methadone dose stability for one week prior to fetal monitoring was defined to reflect the achievement of steady state plasma methadone concentrations after 5 half lives, or 5 to 7 days (US Dept of Health and Human Services, 2005; Srivastava and Kahan, 2006). Thirty two weeks gestation was used to define a period of drug abstinence or drug use due to the tendency of some substances to linger in tissue reservoirs (Moeller et al., 2008).

2.2 Procedure

Data collection involved two 1-hour fetal monitoring sessions on the same day during the 36th week of gestation. The initial monitoring session took place at the time of trough maternal methadone level at 9–10 AM (just before oral dose) and the second at the time of peak maternal methadone level at 1–2 PM (2 ½ hours after oral dose) for participants in the two methadone-maintained groups. Acute methadone exposure has been found to differentially affect fetal neurobehaviors (Jansson et al., 2005). For the NM/A group, monitoring occurred at the same times of day to control for potential fetal variations. Participants were asked to eat a meal and refrain from cigarette smoking for 2 hours before each session. Recent cigarette smoking was evaluated at both sessions by breathalyzer testing for carbon monoxide (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 which would have disqualified

participation 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 1 drink. Urine was obtained for toxicology at both sessions, and women with positive urine toxicology for illicit substance use or licit substance misuse indicating recent drug use and acute fetal drug exposure did not undergo fetal testing; this occurred in one participant in the MM+Poly group. Participant perceived symptomatology indicative of opiate withdrawal was surveyed at each test session using the Subjective Opiate Withdrawal Scale (SOWS; Handelsman et al., 1987). SOWS scores below mid-teens reflect minimal or no symptomatology suggestive of withdrawal.

2.2.1 Fetal measures—Fetal data were collected using a Toitu (MT325, Tokyo, Japan) 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 band-passing frequency components of the Doppler signal that are associated with FHR and maternal somatic activity. 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 offline using customized software (James Long Company, Caroga Lake, NY). Digitized FHR data underwent error rejection procedures based on moving averages of acceptable values as needed.

Fetal variables included 2 cardiac measures: FHR and FHR variability (root mean squared) computed for each 1-minute epoch averaged over time. FM measurement was based on the actograph signal, which ranges from 0 to 100 in arbitrary units. A movement bout was considered to begin when the first spike of the actograph attained an amplitude of 15 units, and ended when there was a cessation of 15 unit signals for at least 10 seconds. The number of movement bouts was counted, and the duration of each movement measured. Total motor activity was computed as the number of movement bouts multiplied by the mean movement duration (seconds) divided by 3600 (number of seconds per recording), yielding the total proportion of time the fetus spent moving.

2.2.2. Infant measures—All infants were delivered at the same hospital. All methadone-exposed infants in the two Methadone groups were hospitalized for a minimum of 4 days for observation for NAS. Infants with negative toxicology screening at birth and born to a mother not receiving methadone (NM/A group) were hospitalized for a minimum of 2 days. All infants received NAS scoring every 4 hours for their entire hospitalization using a modified Finnegan scale (Jansson et al., 2009b). Scoring was conducted by nursing staff experienced in the care of drug-exposed neonates and unaware of the infant's participation in the study.

2.3 Data Analysis

One-way analysis of variance (ANOVA), with planned contrasts and Chi-square analyses as appropriate were used to compare maternal and infant characteristics. Repeated Measures ANOVA with planned contrasts were used to evaluate overall main effects and isolate differences between pairs of groups at both recordings. A linear mixed model was used to evaluate overall changes in parameters between the first (Time 1) and second (Time 2) recordings, and evaluate pairwise group differences in the slopes. Given the small sample size of each group and the resultant magnitude of the mean difference that would be required to generate significant (i.e., $p < .05$) differences for each contrast, we also report results of analyses that neared significance ($p < .10$).

3. RESULTS

3.1 Maternal characteristics

Maternal characteristics are presented in Table 1. The groups did not differ on age, parity, or education level. There were significantly more non-Hispanic-White women in the MM+Poly group and more African-American women in the NM/A group. Most women (82%) smoked cigarettes and there was a trend ($p < .10$) level difference among groups in the number of cigarettes reported smoked per day, with the least reported smoking in the NM/A group. However, CO levels at the time of fetal testing did not differ among groups. There were no differences in proportion of SSRI-maintained women between groups. No participant reported subjective feelings of withdrawal as indicated by SOWS screening.

Maternal drug treatment and drug use characteristics are presented in Table 2. There were no differences in the duration of time spent in treatment among groups, and methadone dose did not differ between the two Methadone groups. On average, women received between 15 and 21 urine toxicology screens during treatment with the MM/A group receiving more screening than either other group. As expected, the percent of urine toxicology screenings positive for illicit substances was highest in the MM+Poly group. There were no differences detected among groups for age at first drug use, age at regular use (3x/week or more), or number of years of regular drug use, suggesting that women in each group were similarly exposed to drug use and factors related to drug use prior to treatment entry.

3.2 Fetal Measures

One instance of fetal data at peak and three at trough were of insufficient quality to allow variable computation for two participants in the MM+Poly group (1 fetus shared both peak and trough insufficiency) and one in the NM/A group.

3.2.1. Group effects—Repeated measures analysis of variance revealed significant main effects of group assignment for each fetal measure, including FHR ($F(2, 43) = 3.62, p < .05$), FHR variability ($F(2, 43) = 4.85, p < .05$), and motor activity ($F(2, 43) = 3.87, p < .05$). Table 3 presents univariate contrasts comparing each group pairing for trough/morning and peak/afternoon values; values at peak and trough are presented in Figures 1a–1c. At trough/morning there were no significant differences between any two groups for the fetal cardiac measures, although there was a trend ($p < .10$) toward significant differences between the MM/A and the NM/A groups for FHR, with a tendency for lower FHR in the methadone-exposed group. Regarding motor activity, the MM+Poly group did not differ significantly from either of the currently abstinent groups (MM/A, NM/A), but the MM/A group exhibited significantly less motor activity than the NM/A.

In contrast, there were consistent significant differences in peak/afternoon fetal cardiac measures, with both Methadone-exposed groups exhibiting decreased FHR and FHR variability as compared to the Non-methadone group. Also, the MM/A group, but not the MM+Poly group fetuses spent less time moving than the NM/A group fetuses.

3.2.2. Group differences over time—Examination of Figures 1a and 1b illustrate the impact of poly-drug use above and beyond methadone exposure alone, and the differences between both methadone groups and the non-methadone group on the fetal cardiac measures. There were significant overall effects for Time for FHR ($F(1, 45) = 10.57, p < .01$) and FHR variability ($F(1, 45) = 8.76, p < .01$). The apparent differences in slopes by group are confirmed by significant Group by Time interactions for both variables ($ps < .05$). As would be expected, the NM/A group did not show any significant changes in fetal measures from morning to afternoon ($ps > .10$), which dilutes detection of overall

differences. Pairwise comparisons examining differences in slopes among groups indicate that the MM+Poly group showed significantly greater decline in FHR than both the NM/A ($t(45) = -2.68, p < .05$) and the MM/A group ($t(45) = -2.10, p < .05$). With respect to FHR variability, the MM+Poly group showed significantly greater decline than the NM/A group ($t(45) = -3.03, p < .01$) and there was a trend difference with the MM/A group ($t(45) = -1.70, p < .10$). The differences in slope between the MM/A and NM/A groups did not attain significance for FHR or FHR variability. Slopes for FM activity (Figure 1c) did not differ among any groups.

3.2.3. Clinical ratings—Paper fetal heart rate tracings were evaluated by a Maternal-Fetal medicine specialist, who was blind to group designation, for clinical ascertainment of reactivity/non-reactivity using standard clinical criteria based on the presence or absence of accelerations in fetal heart rate. Most tracings were reactive during the trough/morning recording: MM+Poly (100%); MM/A (89%); and NM/A (92%); there were no differences among groups ($\chi^2(2, N = 49) = 2.90, ns$). There was no difference in reactivity in the peak/afternoon recording for the NM/A group (92%), but both the methadone groups showed near-significant reductions in reactivity to 56% (MM+Poly) and 61% (MM/A) at peak drug level ($X^2(2, N = 49) = 5.78, p = .055$).

3.3 Infant Outcomes

Neonatal characteristics are presented in Table 4. Neither anthropometric measures nor Apgar scores differed by exposure group. One infant in the NM/A group was delivered mildly preterm (i.e., 36 weeks, 5 days). There was an overall trend level difference in gestational age at delivery among groups ($F(2, 47) = 2.88, p < .10$). Planned contrasts indicated a significant difference between the two Methadone-exposed groups, with the MM+Poly group delivering almost one week earlier ($t(34) = -2.38, p < .05$) than the MM/A group. One infant in the NM/A group developed a significant postnatal condition (i.e., necrotizing enterocolitis) so hospitalization duration is not included in the group means. There were no other significant infant medical complications detected after delivery.

As expected, none of the NM/A group infants received treatment for NAS; however nearly twice as many of the infants in the MM+Poly group received pharmacotherapy for more severe NAS presentation as compared to the MM/A group ($X^2 = 4.30, p < .05$). However there was no difference between the Methadone-exposed groups in the number of days of pharmacotherapy required to treat NAS, indicating that while there was a difference in incidence of NAS between the two Methadone-exposed groups, there was no difference in severity of NAS among affected infants.

4. CONCLUSION

The original hypothesis of a continuum of impairment, such that maternal poly-drug use during pregnancy can potentiate effects of methadone exposure on the developing fetus and newborn infant, was partially supported. Infants in the MM+Poly group delivered nearly one week earlier and were twice as likely to receive treatment for NAS than the MM/A group, despite the fact that the maternal dose in each group was equivalent. Although all infants were delivered at term, there is increasing evidence of the heterogeneity of term births, including increased morbidity and mortality for infants born in the 38th gestational week, the mean age at delivery for the Methadone + poly-drug group, as compared to later gestational ages (Reddy et al., 2011). These findings are consistent with a multiple risk model that posits that the likelihood of negative infant outcome is proportional to the complexity of maternal exposures. Mechanisms may include direct toxic effects of the substances on the developing fetus and indirect effects via modulation of the maternal autonomic nervous system. With respect to the latter possibility, we have previously reported that NAS severity

is related to the degree of maternal autonomic lability to methadone dosing and that NAS is, in part, a result of fetal adaptation to a continually changing intrauterine milieu (Jansson et al., 2007). Exposure to additional substances, each of which exerts independent effects on the developing fetus, may potentiate maternal autonomic lability. Alternatively, poly-drug use may simply be a marker for more complicated and maladaptive influences in women's lives. Such factors may act in additive manner to generate poorer outcomes or in a multiplicative way to potentiate NAS expression (Vrekoussis et al., 2010; Lester and Lagasse, 2010). The most straightforward explanation, perhaps, is that other substances may generate features of infant neurobehavioral dysfunction that mimic and overlap, independently or by synergistically, with NAS symptoms. The lack of true distinction between NAS expression and neurobehavioral dysfunction may be the link between NAS severity and adverse infant development (D'Apolito, 2001). Further research is necessary to differentiate NAS symptoms in multiply- vs. methadone only-exposed infants, which could result in new medication strategies to treat multiply-exposed infants.

The current results also partially support the position that the origins of potentiated poly-drug effects at birth can be detected during the fetal period. For fetal cardiac measures, there were no significant differences among groups at baseline, which corresponds to methadone trough for the two Methadone-exposed groups. Differences at trough may reveal more chronic consequences of exposure status and as such, we were unable to detect cardiac differences related to these exposure variations. At the time of peak maternal methadone levels, reflective of acute exposure, both Methadone groups showed significant depression in both fetal cardiac measures compared to the Non-Methadone group. More relevant to the current question, however, is whether methadone differentially affected fetal cardiac patterns depending on exposure group as evidenced with respect to changes from peak to trough. It did significantly so with respect to suppression of fetal heart rate, and marginally so for fetal heart rate variability ($p < .10$). Changes in slope were also significantly different between the NM/A group and the MM+Poly group for fetal heart rate and variability. Since there was no intervention, any changes in the NM/A group would reflect normal diurnal variation. The significant changes in slope for both fetal cardiac measures between the non-methadone group and the MM+Poly group, but not the MM/A group may be only a function of degree that the study was under-powered to detect, or further demonstrate the potentiating effect that additional substance use has on methadone administration.

The pattern of results for FM activity was quite different. Fetuses exposed only to methadone (MM/A) showed significantly less FM activity as compared to the non-methadone (NM/A) group at *both* peak and trough. However, there were no differences in slopes (i.e., the effect of methadone per se) from peak to trough. Together these findings suggest a more chronic effect of methadone exposure on motor suppression, although there is no ready explanation as to why a difference between the NM/A and the MM+Poly group was not detected. It is possible that the on-going exposure to other substances may have exerted stimulating effects on the fetal motor system that partially counterbalance the dampening effects of methadone.

Limitations of this study reflect the difficulties in selecting an appropriate control group for studies of prenatal drug-exposure. Measurement challenges include lack of complete ascertainment and evaluation of both licit and illicit drugs during pregnancy, including no information regarding fetal exposure to poly-drugs by women in any of the three groups prior to the enrollment period of 28 weeks gestation. Maternal report of drug use prior to treatment is fraught with difficulties in both accuracy of recall and truthful disclosure of illegal activity during pregnancy. Our alternate approach was to ascertain equivalence among groups by collecting information regarding pre-pregnancy history characteristics, such as maternal age at first illicit drug use and duration of regular use. The lack of

differences on these proxy measures among groups suggests that fetuses in the three groups were similarly poly-drug-exposed early in pregnancy. However, without recruitment earlier in pregnancy it is not possible to ascertain conclusively that there were no differences in drug use prior to 28 weeks gestation.

During the period of study participation, complete ascertainment of every instance of maternal drug use was not possible, even with frequent urine toxicology screening, and the poly-drug use mix of licit and illicit substances may have differed among the groups in systematic ways that we could not capture. There is some evidence to this effect such that there was a near significant difference in the number of cigarettes women reported using per day. The lack of any group differences in CO levels at the time of fetal testing reduces our concern that smoking was an acute concurrent confound on the fetal measures, but it does not dispel the possibility of more chronic effects of smoking patterns on longer term outcomes, and particularly with respect to gestational duration. In addition, although SSRI use was common enough to be evaluated as a potential modifier of effects, exposures to other individual substances were too infrequent to compile for analysis and may have exerted unknown effects. Moreover, drug choice may reflect non-random variation in other features of maternal functioning that may have implications for the developing fetus, including maternal psychopathology. In contrast, our use of presumed positive urine toxicology screening and drug treatment noncompliance reflect restrictive criteria that may not be entirely accurate in all instances as proof of relapse to drug use. As a partial consequence, perhaps the most important limitation of this study is the small group sample sizes, particularly in the non-methadone and currently abstinent group. However, our ability to detect significant differences on a number of measures suggests that the magnitude of the differences are fairly large and indicate that larger samples in each group would thereby increase the ability to detect differences between the two methadone-exposed groups that did not attain significance in this study.

The results affirm the need for comprehensive obstetric, pediatric, and substance abuse treatment that specifically addresses opioid and non-opioid drug use and other factors related to maternal drug dependency in this population. The results also support the need for intensified treatment for women who abuse other substances while on methadone therapy. Policies that reduce the dose of methadone and/or otherwise de-intensify or discontinue drug treatment for women who continue to use other drugs in addition to methadone during pregnancy may be contraindicated by the results presented here, which indicate that offspring of poly-drug using women in methadone treatment may be most at risk for altered development.

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(1a)

* $p < .05$

(1b)

 $^{\wedge}p < .10$; $^{**}p < .01$

(1c)

Figure 1. Fetal data collected at Time 1 (trough methadone) and Time 2 (peak methadone) in the two Methadone-exposed groups and at comparable morning and afternoon times in the Non-methadone group. Notations refer to significance of differences in slope

- The Methadone+Poly-drug group showed significantly greater suppression in fetal heart rate (bpm) from Time 1 to Time 2 as compared to both the Non-Methadone and the Methadone only groups.
- The Methadone+Poly-drug group (MM+Poly) showed significantly greater suppression in fetal heart rate variability from Time 1 to Time 2 as compared to the Non-Methadone group (NM/A) and a trend level difference as compared to the Methadone only (MM/A) group in heart rate variability from Time 1 to Time 2.
- Although there were significant differences at each recording between the Non-methadone and Methadone+Poly drug groups (see Table 3), in fetal motor activity (i.e., the proportion of time engaged in motor activity during the 1-hour recording), slopes did not differ over time.

Table 1

Maternal characteristics by drug use group

	Methadone + Poly (MM+Poly-) n = 18	Methadone (MM/A) n = 19	Non-methadone (NM/A) n = 12
Maternal age (years)	29.22	28.47	30.25
Education level (years completed)	11.94	11.11	11.17
Race [*]			
Caucasian (%)	16 (88.9)	10 (52.6)	4 (33.3)
African American (%)	2 (11.1)	8 (42.1)	8 (66.7)
Hispanic (%)	0 (0.0)	1 (5.3)	0 (0.0)
Parity	1.83	1.89	3.17
Smoker (%)	17 (94.4)	15 (78.9)	8 (66.7)
Number of cigarettes smoked / day [^]	14.18	12.60	7.25
SSRI prescribed (%)	4 (22.2)	5 (26.3)	6 (50.0)

[^]
 $p < .10$;^{*}
 $p < .05$

Table 2

Mean values for maternal drug treatment and use characteristics by group

	Methadone + Poly (MM +Poly) n = 18	Methadone (MM/A) n = 19	Non- methadone (NM/ A) n = 12
Treatment duration (days)	123.89	158.68	132.08
Methadone dose (mg)	80.00	78.16	0.00
Number of urine toxicology screens during treatment	16.06	21.47*	15.58
Percent positive urine toxicology screens during treatment	29.64**	14.37	15.80
Age at first use (years)	14.11	16.00	14.33
Age at regular use (≥ 3 x/wk; years)	18.56	19.47	18.67
Duration of regular use (≥ 3 x/wk; years)	10.69	9.05	11.83

Note.

* $p < .05$, Methadone group significantly different than other two,;

** $p < .01$., Methadone + Poly group significantly different from other two,

Table 3

Planned One-Way ANOVA contrasts between each group across both recordings

	Fetal Heart Rate	Fetal Heart Rate Variability	Motor Activity
Trough/Morning			
Methadone + Poly-drug vs. Methadone	0.70	0.50	0.99
Methadone + Poly-drug vs. Non- methadone	-1.22	-0.82	-1.22
Methadone vs. Non-methadone	-1.89 [^]	-1.29	-2.14 [*]
Peak/Afternoon			
Methadone + Poly-drug vs. Methadone	-1.11	-1.45	1.38
Methadone + Poly-drug vs. Non- methadone	-3.17 ^{**}	-4.35 ^{***}	-1.53
Methadone vs. Non-methadone	-2.23 [*]	-3.13 ^{**}	-2.82 ^{**}

[^]
 $p < .10$;^{*}
 $p < .05$;^{**}
 $p < .01$;^{***}
 $p < .001$

Table 4

Infant characteristics by drug use group

	Methadone + Poly (MM +Poly) n = 18	Methadone (MM/A) n = 19	Non-methadone (NM/A) n = 12
Birth weight (g)	2909.11	3064.53	3144.50
Length (cm)	48.91	48.74	49.93
Head circumference (cm)	32.72	33.56	33.33
1-min Apgar	8.00	8.33	8.00
5-min Apgar	8.83	9.06	8.83
Gestational age (wks)	38.60*	39.58	39.08
NAS pharmacotherapy (%)	15 (83.3)*	8 (42.1)	0 (0.0)
Mean(<i>sd</i>) total days of pharmacotherapy required to treat NAS for those infants requiring pharmacotherapy for NAS	10.67 (6.58)	13.14 (11.17)	

Note. The Methadone + Poly (MM+Poly) group had significantly lower gestational age and greater NAS treatment required (* $p < .05$) than the Methadone only (MM/A) group.