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MATERNAL DEPRESSION AND PRENATAL EXPOSURE TO METHAMPHETAMINE: NEURODEVELOPMENTAL FINDINGS FROM THE INFANT DEVELOPMENT, ENVIRONMENT, AND LIFESTYLE (IDEAL) STUDY

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Abstract

Background—Maternal depression is associated with a higher incidence of behavioral problems in infants, but the effects of maternal depression as early as 1 month are not well characterized. The objective of this study is to determine the neurobehavioral effects of maternal depression on infants exposed and not exposed to methamphetamine (MA) using the NICU Network Neurobehavioral Scale (NNNS).

Methods—Four hundred twelve mother–infant pairs were enrolled (MA = 204) and only biological mothers with custody of their child were included in the current analysis. At the 1-month visit (n = 126 MA-exposed; n = 193 MA-unexposed), the Beck Depression Inventory-II (BDI-II) was administered, and the NNNS was administered to the infant. Exposure was identified by self-report and/or gas chromatography/mass spectroscopy confirmation of amphetamine and metabolites in newborn meconium. Unexposed subjects were matched, denied amphetamine use, and had negative meconium screens. General Linear Models tested the effects of maternal depression and prenatal MA exposure on NNNS, with significance accepted at $P < .05$.

Results—The MA group had an increased incidence of depression-positive diagnosis and increased depression scores on the BDI-II. After adjusting for covariates, MA exposure was associated with increased arousal and handling scores, and a decreased ability to self-regulate. Maternal depression was associated with higher autonomic stress and poorer quality of movement.

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No additional differences were observed in infants whose mothers were both depressed and used MA during pregnancy.

Conclusions—Maternal depression is associated with neurodevelopmental patterns of increased stress and decreased quality of movement, suggesting maternal depression influences neurodevelopment in infants as young as 1 month.

Keywords

amphetamine; drug; antenatal

INTRODUCTION

Methamphetamine (MA) use continues to be a significant public health problem in the United States. In 2008, the Substance Abuse and Mental Health Services Administration (SAMHSA) reported the number of Americans who had tried MA in their lifetime was over 12.5 million.[1] There is little information about MA use during pregnancy, but available data suggest substance abuse by pregnant women continues to be a significant public health problem. The 2008, SAMHSA report found 5.1% of pregnant women ages 15–44 years used illicit drugs during pregnancy[1] and data from the Treatment Episode Data Set (TEDS), a national database obtained from admissions to substance abuse treatment centers, recorded a twofold increase in admissions due to MA between 1997 and 2007.[2] The TEDS data also found that MA has emerged as the primary substance causing women to seek drug treatment during pregnancy,[3] accounting for one quarter of all admissions of pregnant women to treatment centers.

Depression is a consistent finding in methamphetamine using women. Zweben et al. reported 68% of women seeking outpatient drug treatment reported a history of feeling depressed and 28% reported attempting suicide at some point in their lifetime.[4] The depression frequently reported with MA users may be related to preexisting depressive symptoms or secondary to MA-induced effects. Long-term MA use has been associated with more severe psychiatric symptoms, a finding possibly attributable to a greater reduction of dopamine transporter density in the brain.[5] Volkow et al. found decreased dopamine D2 receptor levels in the brain of MA users, which persisted for several months after abstinence.[6] Given that decreased dopamine has been linked with depression,[7] women who use MA during pregnancy, or those recently abstinent, are at increased risk for depressive symptoms.

Pregnancy and the postpartum period are times of significant vulnerability to depression. Bennett et al. found a 12% prevalence of depression during the second and third trimesters.[8] In addition, the incidence of postpartum depression is reported in 10–22% of women.[9] There are numerous possible factors contributing to postpartum depression including a precipitous decrease in estrogen,[10] progesterone, and prolactin[11] after childbirth, and depressed levels of thyroid hormones.[12] Women are especially vulnerable to postpartum depression if they have a personal[9] or family history of depression.[13] Pregnancy-related risk factors for postpartum depression include unplanned pregnancy and unemployment,[14] which are often associated with substance abusing women.

Adverse effects of maternal depression on child development have been reported. Infants as young as 3 months can detect a depressed affect in their mothers and by 18 months maternal depressive symptoms are associated with decreased verbal interaction, increased time playing alone, less competence in object concept tasks, and insecure attachment. These findings at 18 months are noted even though a majority of the women no longer reported depressive symptoms[15, 16] suggesting children are vulnerable to maternal depressive

symptoms during the first 3 months of life and are at risk for long-term developmental delays.

Data regarding the effects of maternal depression on infants younger than 3 months are limited. Diego et al. investigated the effects of prepartum and postpartum depression on 1-week-old infants and found newborns of mothers with prepartum and postpartum depressive symptoms had elevated urine cortisol and norepinephrine levels and lower dopamine levels.[17] These biochemical changes are consistent with prepartum elevations in maternal cortisol and norepinephrine of depressed women,[18] suggesting maternal biochemical influences on both the fetus and early newborn. In addition, infants of mothers with depression during pregnancy have greater relative right frontal electroencephalogram asymmetry,[17] which has been linked with negative affect. Collectively, these findings suggest it is possible for maternal depression to adversely affect infants in the early neonatal period.

The Infant Development, Environment, and Lifestyle (IDEAL) study is a controlled, longitudinal investigation of MA-exposed children in diverse populations and geographic locations. We have previously reported preliminary results after 1 year of recruitment that prenatal MA exposure is associated with decreased arousal and increased stress signs in the newborn period.[19] We also found maternal depression, regardless of MA exposure status, was associated with decreased arousal and increased stress during the newborn period when analyzing only a partial sample set.[20] This previous study utilized the Addiction Severity Index, which consisted of dichotomous responses, to assess for maternal depression at the time of delivery. It also did not include the full sample set as is presented here. Because both MA using and postpartum women are susceptible to depression, in this study we hypothesized there would be negative effects of concurrent prenatal MA exposure and postnatal maternal depression on neurodevelopment of 1-month-old infants in the complete dataset.

MATERIALS AND METHODS

STUDY DESIGN

The IDEAL study is a multisite, longitudinal study investigating the effects of prenatal MA exposure on child outcome. Detailed recruitment methods for the IDEAL study have been reported previously.[21] Briefly, from September 2002 to November 2004, subjects were recruited at the time of delivery from seven hospitals in four geographically diverse, collaborating centers in the following cities: Los Angeles, CA; Des Moines, IA; Tulsa, OK; and Honolulu, HI. All women delivering at each of the four clinical sites were approached (n = 26,999), screened for eligibility (n = 17,961), and consented to participate in this 3-year study (n = 3,705). A postpartum mother was excluded if she was <18 years of age, used opiates, lysergic acid diethylamide, phencyclidine, or cocaine-only during her pregnancy, institutionalized for retardation or emotional disorders, of low cognitive functioning, overtly psychotic or a documented history of psychosis, or non-English speaking. Exclusion criteria for the infants included: critically ill and unlikely to survive, multiple birth, major life-threatening congenital anomaly, documented chromosomal abnormality associated with mental or neurological deficiency, overt clinical evidence of an intrauterine infection, and sibling previously enrolled in the IDEAL study.

MA exposure was determined by self-reported MA use during this pregnancy and/or a positive meconium screen and gas chromatography/mass spectroscopy (GC/MS) confirmation. Unexposed subjects were defined as denial of MA use during this pregnancy and a negative GC/MS for amphetamine and metabolites.

The study was approved by the Institutional Review Boards at all participating sites and signed informed consent was obtained from all subjects. A National Institute on Drug Abuse Certificate of Confidentiality was obtained for the project that assured confidentiality of information regarding the mothers' drug use, superseding mandatory reporting of illegal substance use.

PARTICIPANTS

The longitudinal follow-up sample included all MA-exposed infants and mothers ($n = 204$) and unexposed dyads ($n = 208$) who were matched on maternal race, birth weight, type of insurance, and education. Because we are analyzing the effect of maternal depression at the 1-month visit, only biological mothers ($N = 319$) with custody of their child were included in the analysis.

PROCEDURES

After consent was obtained, a medical chart review and a recruitment Lifestyle Interview [22, 23] were performed to acquire information about prenatal substance use, maternal characteristics, and newborn characteristics. Socioeconomic status (SES) was determined using Hollingshead V, an index that ranks SES based on occupation and years of education.[24] Meconium was collected in the nursery on all infants of consented mothers. Information on the collection procedures and analysis of the meconium samples was published previously.[21]

Depression status was obtained at the 1-month visit using the Beck Depression Inventory-II (BDI-II). The BDI-II is a 21-item self-report instrument measuring the intensity of depression in the primary caretaker.[25] The BDI-II is a well-established measurement with an α reliability coefficient of .92 and construct validity of $r = .93$ in an out-patient population.[26] It also has an internal consistency coefficient of .80 across ethnic groups and aging populations.[27] A single summary score for level of depression is obtained by aggregating item scores and then dichotomized into depressed (score of ≥ 14) and not depressed groups.

The NICU Network Neurobehavioral Scale (NNNS) exam was administered to the infant at the 1-month visit by certified examiners masked to MA exposure status. The NNNS is a standardized neurobehavioral exam for both healthy and at-risk infants. The NNNS provides an assessment of neurological, behavioral, and stress/abstinence neurobehavioral functioning.[28] The neurological component includes active and passive tone, primitive reflexes, and items that reflect the integrity of the central nervous system and maturity of the infant. The behavioral component is based on items from the Neonatal Behavioral Assessment Scale,[29] modified to be sensitive to putative drug effects. The stress/abstinence component is a checklist of "yes" or "no" items organized by organ system based primarily on the work of Finnegan.[30]

The NNNS items are summarized into the following scales: Habituation, Attention, Arousal, Regulation, Handling, Quality of Movement, Excitability, Lethargy, Nonoptimal Reflexes, Asymmetric Reflexes, Hypertonicity, Hypotonicity, and Stress/Abstinence. The estimated means of the NNNS summary scores for the exposed and unexposed groups regardless of biological caretaker status have been previously reported.[19]

STATISTICAL ANALYSIS

Maternal and infant characteristics were assessed by one-way analysis of variance or chi-square. The independent effects of MA exposure and maternal depression were assessed using General Linear Modeling (GLM). The GLM models were adjusted for prenatal

alcohol, tobacco, marijuana, and cocaine exposure, Hollingshead SES, maternal weight gain, 5-min Apgar, gender, and site. Covariates were selected based on conceptual reasons, published literature, and maternal and newborn characteristics from Tables 1 and 2 that differed between groups. All covariates were significantly different by MA exposure status. The interaction effect of MA exposure and maternal depression was also tested in the model. Significance was accepted at $P < .05$.

RESULTS

MATERNAL AND INFANT CHARACTERISTICS

Maternal characteristics by MA exposure status of the 319 biological mothers are reported in Table 1. As expected by study design, there were no group differences in race, insurance status, and education level. No differences were observed with number of prenatal visits, maternal age, height, and weight before pregnancy. Relative to the unexposed group, mothers in the exposed group were more likely to have a lower SES, greater likelihood of depression-positive diagnosis, increased depression scores on the BDI-II, and greater weight gain during pregnancy. Possible reasons for weight gain were previously reported.[31]

Table 2 shows the neonatal birth characteristics. No significant differences between the exposed and unexposed infants were found in gender, birth weight, length, head circumference, gestational age, and the 1-min Apgar score. MA-exposed infants were more likely to have a lower 5-min Apgar score than the unexposed infants.

PRENATAL DRUG EXPOSURE

Prenatal drug exposure is also shown in Table 2. Since cocaine exposure was an exclusion criteria for the unexposed group, there were no infants in the unexposed group with cocaine exposure versus infants in the exposed group. Exposed infants were more likely to be exposed to tobacco, alcohol, and marijuana.

MA EXPOSURE STATUS AND MATERNAL DEPRESSION EFFECTS ON NNNS

Table 3 shows the unadjusted summary scores for the effects of MA exposure on the NNNS. After adjusting for covariates, exposure was associated with higher arousal and higher handling scores, and decreased ability to self-regulate. A higher score in arousal is indicated by an infant who is easily aroused to fuss and cry, and highly active while being handled or left alone.[32] Handling is scored as the type and amount of maneuvers that were necessary to keep the infant in the appropriate state during the exam, with low scores requiring minimal input from the examiner.[32] High handling scores are consistent with increased arousal scores. Regulation is scored as the capacity to cope with the demands of the examination, respond to soothing by the examiner, and self-soothe.[32] Lower scores indicate poorer regulation.

Unadjusted means of the NNNS summary scores for maternal depression are also shown in Table 3. Regardless of exposure status, after adjusting for covariates, maternal depression was associated with increased autonomic stress scores and decreased quality of movement. The autonomic stress score assesses numerous functions in the infant including sweating and regurgitation. Decreased quality of movement scores indicate the infant is jittery, with little or no smooth movement of the arms and legs, startles easily, and has high overall activity. Prenatal MA exposure combined with maternal depression was not associated with any additional developmental outcomes.

DISCUSSION

We found an increased incidence of depression-positive diagnosis and depression scores on the BDI-II in the MA group relative to the unexposed group. MA was associated with increased arousal and handling scores and decreased ability to self-regulate, whereas maternal depression was associated with increased autonomic stress scores and decreased quality of movement in the infants. These findings suggest maternal depression can affect neonatal neurodevelopment as early as 1 month, regardless of exposure status.

Maternal depression was more prevalent in our MA-using mothers than the control group. This finding is consistent with previous reports that MA use is associated with a higher incidence of depression and depressive symptoms than nonusers.[33,34] MA use alters neurotransmitters in the brain that are associated with mood and emotional states. Prolonged use of MA leads to damaged neurotransmitter receptors and presynaptic reuptake mechanisms, and is theorized to be associated with persistent depressive symptoms, even after abstinence.[5,35] Other factors that may have contributed to the higher incidence of depression in the MA group include lower SES and higher rates of smoking in the MA group. Numerous investigators have reported that low SES is associated with depression.[13, 36] Additionally, smoking has been associated with maternal depressive symptoms.[37] Thus, numerous factors may contribute to the increased rate of depression in the MA-using mothers.

Our findings that maternal depression affects infant neurodevelopment as early as 1 month is consistent with previous work linking maternal depression with decreased cognitive development,[38] lower scores in motor development,[39] increased crying at 3 months of age,[40] and child behavioral problems in boys up to age 5 years.[41] Researchers have found depressed mothers are less responsive[42] and emotionally unavailable[43] to their children compared to nondepressed mothers, and that infants of depressed mothers are more likely to establish an avoidant attachment style[44] and poor emotion regulation.[45] This lack of contact and insecure attachment style can impede the activation and growth of neurotransmitters, possibly accounting for the delays in infant neurodevelopment. Given that depression and MA use have been associated with differences in infant development independently, we expected depressed MA-using mothers would have infants with less-favorable development relative to infants of MA-using mothers who were not depressed. Contrary to our hypothesis, we did not find that the combination of depression and prenatal MA use had additive effects on infant neurodevelopment. Our findings are consistent with data from infants exposed to maternal depression and cocaine, another sympathomimetic agent. Salisbury et al. found no significant differences on infant outcome between infants prenatally exposed to cocaine and maternal depression and infants prenatally exposed to cocaine but not maternal depression.[46]

There are several limitations to the current investigation; therefore, these findings should be interpreted with caution. We included only biological mothers; as a result, our sample size was limited to those infants who remained in the custody of their biological mothers and did not allow for examination of the effects of paternal or alternate caregiver depression. Additionally, many of our MA-exposed infants were placed in foster care or the care of relatives; therefore, a larger sample size is required to determine differences in the depressed mothers from the MA group compared to the depressed mothers in the control group. Although the BDI-II is highly accurate in identifying depression, it does not differentiate between postpartum depression and major depression. It is possible that the results may have differed given further clarification as to the specific type of maternal depression experienced.

CONCLUSION

In summary, we found that maternal depression can impact infant neurodevelopment as early as 1 month. These findings, in combination with the efficacy of numerous depression treatments,[47–50] demonstrate the need for intervention in mothers with depression. Due to finding differences at such an early age, maternal interventions are necessary at the first sign of depressive symptoms including negative affect, a noticeable increase or decrease in sleeping patterns, increased anxiety, or a lack of motivation. Implementing a standardized depression-screening tool that is easy to administer and score by pediatric and obstetric care providers would assist in early identification of mothers with depression. Long-term follow-up is necessary to determine if treating maternal depression early leads to improved parenting skills and overall healthier infant development over time.

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TABLE 1

Characteristics of biological mothers in the methamphetamine-exposed and -unexposed groups

	Mean (*SD*)/Number (Percent)		
	Exposed (*N* = 126)	**Unexposed (*N* = 193)**	***P*-value**
Race			.895
White	51 (40.5%)	77 (39.9%)	
Hispanic	31 (24.6%)	41 (21.2%)	
Pacific Islander	23 (18.3%)	33 (17.1%)	
Asian	12 (9.5%)	26 (13.5%)	
Black	6 (4.8%)	11(5.7%)	
American Indian	3 (2.4%)	4 (2.1%)	
Other	0 (0.0%)	1 (0.5%)	
Public insurance	105 (83.3%)	152 (78.8%)	.336
Number of prenatal visits	12.91 (7.31)	14.16 (5.50)	.086
Education < 12 years	48 (38.1%)	72 (37.3%)	.872
Low SES, Hollingshead–V	36 (28.6%)	22 (11.4%)	**<.001**
SES Hollingshead Social Position Index	25.02 (8.81)	31.03 (10.13)	**<.001**
Depression-positive diagnosis (BDI-II)	53 (42.1%)	46 (23.8%)	**<.001**
Depression scores (BDI-II)	13.29 (9.51)	9.96 (6.57)	**<.001**
Weight (lbs.)	149.51 (39.64)	145.41 (36.05)	0.342
Weight Gain (lbs.)	45.19 (21.21)	33.85 (15.89)	**<.001**
Height (feet)	5.37 (0.23)	5.32 (0.22)	0.074
Age (yr)	25.71 (5.77)	24.55 (5.54)	0.075

Note: Beck Depression Inventory-II (BDI-II). Maternal characteristics of biological mothers who did and did not use methamphetamine during pregnancy.

TABLE 2

Birth characteristics and prenatal drug exposure of methamphetamine-exposed and -unexposed infants.

	Mean (*SD*)/Number (Percent)		
	Exposed (*N* = 126)	**Unexposed (*N* = 193)**	***P*-value**
Gender			.845
Boy	68 (54.0%)	102 (52.8%)	
Girl	58 (46.0%)	91 (47.2%)	
Birth Weight (g)	3292.34 (576.68)	3294.03 (560.93)	.979
Length (cm)	50.37 (3.24)	50.94 (2.99)	.104
Head circumference	34.06 (1.70)	34.06 (1.80)	.974
Gestational age	38.75 (2.05)	39.01 (1.76)	.244
Apgar 1	7.75 (1.33)	7.99 (0.93)	.050
Apgar 5	8.87 (0.56)	8.97 (0.25)	**.024**
Prenatal cocaine exposure	11 (8.7%)	Exclusion	**<.001**
Prenatal tobacco exposure	99 (78.6%)	51 (26.4%)	**<.001**
Prenatal alcohol exposure	55 (43.7%)	25 (13.0%)	**<.001**
Prenatal marijuana exposure	43 (34.1%)	7 (3.6%)	**<.001**

TABLE 3

NICU Network Neurobehavioral Scale results by methamphetamine exposure status and maternal depression

Measure	Prenatal MA exposure						Maternal Depression					
	Exposed (*n* = 126)		Unexposed (*n* = 193)		*P*		Yes (*n* = 99)		No (*n* = 220)		*P*	
	N	Mean (± *SE*)	*N*	Mean (± *SE*)	Unadjusted	Adjusted	*N*	Mean (± *SE*)	*N*	Mean (± *SE*)	Unadjusted	Adjusted
Attention	114	5.57 (.095)	186	5.65 (.075)	.502	.732	92	5.53 (.110)	208	5.65 (.069)	.355	.644
Arousal	123	4.16 (.059)	192	4.03 (.048)	.078	**.022**	99	4.16 (.068)	216	4.05 (.044)	.146	.362
Regulation	122	5.72 (.064)	192	5.78 (.048)	.467	**.032**	99	5.70 (.064)	215	5.78 (.048)	.336	.433
Handling	118	0.30 (.026)	185	0.29 (.019)	.765	**.019**	92	0.30 (.029)	211	0.29 (.018)	.692	.558
Quality of movement	123	4.88 (.052)	192	4.86 (.042)	.808	.959	99	4.78 (.056)	216	4.91 (.040)	.056	**.038**
Excitability	123	2.64 (.170)	192	2.45 (.147)	.395	.082	99	2.71 (.191)	216	2.44 (.137)	.266	.376
Lethargy	124	3.43 (.136)	192	3.31 (.089)	.462	.292	99	3.42 (.167)	217	3.33 (.081)	.555	.512
Nonoptimal reflexes	124	2.83 (.165)	192	3.14 (.132)	.150	.962	99	2.89 (.168)	217	3.07 (.130)	.408	.722
Asymmetrical reflexes	124	0.37 (.055)	192	0.30 (.038)	.289	.268	99	0.39 (.062)	217	0.30 (.036)	.167	.452
Hypertonicity	123	0.10 (.039)	192	0.12 (.031)	.652	.961	99	0.14 (.052)	216	0.10 (.026)	.394	.367
Hypotonicity	123	0.04 (.018)	192	0.08 (.019)	.184	.361	99	0.06 (.024)	216	0.06 (.017)	.887	.988
Stress/abstinence	123	0.09 (.004)	192	0.09 (.004)	.848	.424	99	0.09 (.005)	216	0.08 (.004)	.111	.053
Autonomic	123	0.09 (.010)	192	0.10 (.010)	.742	.348	99	0.12 (.014)	216	0.09 (.009)	.046	**.008**
CNS	123	0.11 (.008)	192	0.12 (.007)	.513	.656	99	0.12 (.009)	216	0.11 (.006)	.236	.219
Gastrointestinal	123	0.06 (.012)	192	0.07 (.012)	.630	.415	99	0.08 (.016)	216	0.06 (.011)	.462	.261
Visual	123	0.09 (.007)	192	0.08 (.006)	.220	.831	99	0.09 (.007)	216	0.08 (.005)	.343	.511
Skin	123	0.07 (.008)	192	0.07 (.007)	.997	.570	99	0.07 (.009)	216	0.07 (.007)	.792	.577
State	123	0.08 (.010)	192	0.07(.007)	.143	.397	99	0.08 (.011)	216	0.07 (.007)	.803	.939

Note: Methamphetamine (MA). NICU Network Neurobehavioral Scale (NNNS) results based upon prenatal methamphetamine exposure as well as maternal depression.