

ORIGINAL ARTICLE

Perinatal Effects of Combined Use of Heroin, Methadone, and Amphetamine during Pregnancy and Quantitative Measurement of Metabolites in Hair

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Key Words

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Objective: There has been very limited research on the clinical features of newborns exposed to combined use of heroin, methadone, and amphetamine in the uterus. We describe a technique for the quantification of drug metabolites in neonatal hair samples.

Methods: In a tertiary neonatal care center in Taiwan, three neonates whose mothers self-reported heroin abuse with methadone treatment during pregnancy were studied. Involuntary exposure to amphetamine was not suspected before the births. To assess long-term illicit drug exposure during pregnancy, a quantifying technique of gas chromatography/mass spectrometry (GC/MS) for hair samples from neonates was developed to replace current methods for urine and blood specimens.

Results: All three mothers were addicted to heroin and prescribed oral methadone treatment during pregnancy. Two males and one female were born and then admitted to the neonatal intensive care unit because of apparent neonatal abstinence syndrome (NAS) after birth. Additional hypertonicity and cerebral dysfunction were also diagnosed by electroencephalography in one case. Supportive care was given to the neonates, unless special treatments were needed in responding to tachypnea, fetal distress, or withdrawal symptoms. During follow-up periods from 10 months to 15 months, the signs of NAS remained and delays in milestones of

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development were observed. Further follow-up on the infants' neurobehavioral development is necessary. Measurement results of neonates' hair samples revealed high levels of metabolites of heroin, methadone, and amphetamine, reflecting the amount of illicit drug exposure 2–3 months before delivery.

Conclusion: The current study suggested the possibility of polydrug exposure, which was previously unknown in pregnant women in Taiwan. Measurement of neonatal hair samples could provide a basis for clinical evaluation and potential corresponding treatment.

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1. Introduction

As suggested in the 2002/2003 US National Survey on Drug Use and Health, the prevalence of suffering from at least one substance abuse in a year was approximately 11% among adults. In addition, 4.3% of pregnant women aged 15–44 years used illicit drugs, resulting in 172,934 births complicated by maternal use of illicit drugs in the USA.¹ Approximately seven per 1000 adults aged 15–54 years were heroin dependent in Australia, the UK, and Europe. Among them, around 80–90% females were of reproductive age.² The babies of mothers with opiate dependence during pregnancy have increased risks of bloodborne virus infections, including hepatitis B, hepatitis C, and HIV.³ Thus, substance abuse has been listed as one of the 10 high-priority public health issues for the US population in *Healthy People 2010*.⁴

Fetuses exposed to heroin in the uterus have a fluctuating cycle of intoxication and withdrawal after birth. Among the adverse effects of heroin, NAS is the most devastating clinical finding, including the symptoms of tremor, fever, seizure, inability to self-quiet, elevated startle reflex, feeding difficulty, abnormal sleep patterns, and diarrhea. Among neonates who are exposed to opiates in the uterus, 60–90% experience some degree of NAS.^{5–8} Pregnancy complications following substance use decrease development indicators, elevate central nervous system and autonomic nervous system signs, and increase developmental and behavioral problems when the affected babies are growing up. Polydrug use, defined by the use of more than one non-prescribed licit or illicit substance either concurrently or simultaneously, worsens the situation in clinical management.^{8,9}

Methadone, an artificial opiate derivative, has been clinically recommended for the treatment of heroin dependency to pregnant women since the 1970s.⁵ Methadone maintenance treatment gives the benefits of better birth outcomes of neonates, reduction of heroin use during pregnancy, and improvement of overall maternal health, although the side effects of reduced fetal activities, lowered birth weight, and prolonged NAS symptoms exist.⁷ Physical changes during pregnancy complicate the clinical management protocol, and make it more challenging to maintain effective plasma concentration but, in the mean time, minimize the chance of NAS occurring.¹⁰ However, debates on how to minimize added maternal methadone dosage in order to sustain plasma concentration while restricting its impact on mothers and neonates are ongoing.^{5,6,10–14}

Since 2000, opiates (including heroin) have become the top illicit type of drug abused in Taiwan, contributing 70.3% of positive results in urine screening programs conducted by mental health service providers in 2006.¹⁵ Nonetheless, there is scarce research on the combined use of amphetamine and heroin during pregnancy to the health of neonates.⁹ Most of the related studies were performed separately in western countries.^{6,8,16–19} Consequently, for better insight into the issue of polydrug use of amphetamine and heroin during pregnancy, there is a need for research in various study settings. We thus report the clinical courses of three neonatal cases whose mothers confessed that they continued using heroin with methadone replacement therapy during pregnancy, with no idea that amphetamine was foisted until it was identified in the neonate's hair and urine after birth. The methodology of quantifying these illicit drugs in infants' urine and hair was correspondingly developed and reported.

2. Methods

2.1. Study settings

At our tertiary neonatal care center, three pregnant women under suspicion of illicit drug usage were referred from July 1, 2009 to June 30, 2010. They were found addicted to heroin and probably amphetamine during outpatient visits with in-depth interview and routine examinations during pregnancy. Neonatal urine and hair samples were regularly collected for toxicological exams at 1 day old and 14 days after admission. For Case 2, additional urine and hair samples were collected on the 7th day and 16th day after admission. For Case 3, hair was additionally collected after the first day of use of morphine sulfate, after 48 hours, and then 14 days after morphine sulfate was discontinued. The research protocol was approved by the Ethics Committee of Chung Shan Medical University Hospital before the recruitment of cases.

2.2. Measurement methods

Hair samples were bundled and cut as close as possible to the scalp because this is the region of least variation in growth rate, at sites behind the ears, and on the occipital bone within an area of approximately 5 cm². If it cannot be collected by the standard protocol, the alternate site for hair sampling area must be described. The proximal end of the sample must be specified if it was longer than 4 cm. In

addition, sufficient amount of hair (50 mg for about 100 hairs) must be collected to allow primary testing, followed by confirmation of the sample if necessary. The samples should be put in separate paper bags for shipment at room temperature.

The commonly abused drugs in Taiwan suggested by Centers of Disease Control, Taiwan¹⁵ were then measured by gas chromatography/mass spectrometry (GC/MS), according to this modified method for which a simultaneous GC/MS assay was developed and validated.²⁰ Utilization of this new technique made it possible to simultaneously determine four classes of illegal drugs in human hair, including amphetamines (amphetamine, AP; methamphetamine, MA; 3,4-methylene dioxamphetamine, MDA; 3,4-methylene dioxymethamphetamine, MDMA; 3,4-methylene dioxethylamphetamine, MDEA), ketamine (ketamine, K; norketamine, NK), methadone (methadone, MTD; 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, EDDP), and opiates (morphine, MOR; codeine, COD; 6-acetylmorphine, 6-AM). In brief, hair samples (10 mg) were washed, cut, and incubated overnight at 25°C in methanol, then extracted by solid-phase extraction (SPE), and derivatized using heptafluorobutyric acid anhydride (HFBA) at 70°C for 30 minutes. Finally, the derivatives were analyzed by GC/MS in full-scan or selected-ion monitoring (SIM) mode. GC/MS analyses were performed with an Agilent 6890 series automatic injector and GC interfaced to an Agilent 5973 MS operated in electron ionization (EI) mode (Agilent Technologies, Wilmington, DE, USA). Separation was achieved with a 30-m HP-5 MS capillary column (5% phenyl methyl siloxane with 0.25 mm I.D and 0.25 µm film thickness (Agilent Technologies, Palo Alto, CA, USA) and the helium carrier gas flow rate was set at 1 mL/min.

3. Results

3.1. Clinical courses and treatments

All three case mothers self-reported as current heroin users, receiving methadone therapy for 1 week to 4 months, at the respective ages of 38, 31, and 32 years old at delivery for gravida 3 para 3, gravida 5 para 2 SA 1 AA2, and gravida 5 para 1 AA4, separately. Details of their illicit drug use history, clinical features, symptoms/signs, and treatment outcomes are shown in Table 1. One subject self-reported combined use of amphetamine (Case 2). Two cases were heavy smokers of two to three packs a day (Cases 1 and 2), but neither was an alcohol user. All outcomes of prenatal laboratory tests for the cases were within normal range. There were no incidences of toxoplasmosis, other infections (syphilis, varicella, mumps, parvovirus, and HIV), rubella, cytomegalovirus, and herpes simplex (TORCH), hepatitis B, or any other sexually-transmitted infections, but one subject had chronic hepatitis C with symptoms of hyperbilirubinemia, elevated glutamyl oxaloacetic transaminase and glutamyl pyruvic transaminase levels, and an episode of fulminant hepatitis during pregnancy (Case 2). Mild to medium cholecystitis was also noted before delivery. In addition, mitral valve prolapse and a depressive episode of bipolar affective disorder were experienced, with a suicide attempt by

jumping from a high building resulting in multiple fractures. Case 1 reported that throughout the whole pregnancy she was on inhaled corticosteroid therapy for asthma. Particularly, besides a 4-year history of intravenous heroin abuse, Case 3 had been diagnosed as having depression with hallucinations about 9 years before, according to her anamnesis. However, she did not take antidepressants regularly. She claimed that she had received elective termination of pregnancy four times during her first marriage because of the concern of adverse effects from antipsychotics. She had started oral methadone treatments 3 years before and had been on oral methadone 1 mL/day for about 4 months preceding the delivery, but intravenous heroin injection was still used 1 day prior to delivery.

Two males and one female were born at the gestational ages of 35, 34, and 38 weeks, respectively, with labor pain plus preterm premature ruptured of membrane (PPROM), labor pain plus uterine contraction by vaginal delivery (Cases 1 and 2), and via cesarean section due to breech presentation (Case 3). Their Apgar scores at 1 min were 9, 6, and 6, respectively, and 10, 7, and 9 at 5 minutes, respectively. Intrauterine growth restriction (IUGR) with low birth weight was diagnosed in two of them. Ponderal indexes²¹ of 2.02%, 2.72%, and 2.26%, respectively, were identified. On the first day, all neonates were admitted into the neonatal intensive care unit (NICU) for significant NAS, including moderate tremors when undisturbed, high-pitched crying, irritability, tachypnea, and poor feeding with uncoordinated sucking. Only Case 3 had hypertonicity. Serial brain ultrasound exams, electroencephalography, and brainstem auditory evoked potentials were unremarkable for all neonates, except that electroencephalography of Case 3 showed cerebral dysfunction on the 3rd day, but improved after treatment.

Following our protocol for treatment of neonates with maternal heroin exposure in the NICU, each infant was placed in a darkened incubator and the modified Finnegan neonatal abstinence scoring system²² was applied every 4 hours. In Case 1, a condition of tachypnea with 70 respirations/min developed on admittance, therefore nasal continuous positive airway pressure was used for 2 days. In spite of the long duration of maternal heroin addiction, no consecutive scores higher than eight within three times were obtained during the 2 weeks' duration of observation. Thus, the baby received supportive care without particular medication intervention. For Case 2, umbilical cord twice around the neck with moderate to heavy meconium stained and cyanosis was found when labored. Fetal distress and heroin withdrawal symptoms were noted. An oxygen hood was used for the first 2 days. Also, no continuous Finnegan neonatal abstinence scores >8 for three times were observed within 2 weeks. Accordingly, only supportive care was given. For Case 3, following the practical guidelines,¹⁴ drug treatment with phenobarbital proceeded in a loading dose of 15 mg/kg and the remainder administered 6 mg/kg from the first day of admission. Repeated scoring every 4 hours using the modified Finnegan neonatal abstinence scoring system revealed 6–12, after treatment for 1 week. Thus, morphine sulfate was combined with phenobarbital in a dosage of 40 µg/kg every 4 hours. After 5 days of combination treatment with phenobarbital and morphine sulfate, his condition was stabilized. The score decreased

Table 1 Clinical courses, symptoms, signs, and treatment outcomes of the subjects.

Subject	Item	Case 1	Case 2	Case 3
Mother	Illicit drug use history	2 years	2 years	4 years
	Heroin	3 months	1 week	4 months
	Methadone before delivery	Denied	2 years	Denied
Newborn	Amphetamine			
	Gestational age (weeks)	35	34	38
	IUGR	+	+	–
	C/S or NSD	NSD	NSD	C/S
	Perinatal event	PPROM	MAS	–
	Birth weight (kg)	2.100 (10 th percentile)	2.016 (<10 th percentile)	3.184 (10–25 th percentile)
	Body length (cm)	47 (25–50 th percentile)	42 (25–50 th percentile)	52 (75 th percentile)
	Head circumference (cm)	30.5 (10 th percentile)	30 (10 th percentile)	34.5 (25 th percentile)
	High pitched cry	+	+	+
	Tremor	+	+	+
	Excessive sucking	+	+	+
	Tachypnea	+	+	+
	Hypertonicity	–	–	+
	NASS	<8	<8	>8

C/S = cesarean section; IUGR = intrauterine growth restriction, defined as having a birth weight which is more than two standard deviations below the mean or less than 10th percentile of a population-specific birth weight versus gestational age plot;²⁶ MAS = meconium aspiration syndrome; NASS = Neonatal Abstinence Scoring system; NSD = normal spontaneous delivery; PPRM = preterm premature rupture of membrane.

(≤ 7) and phenobarbital was gradually tapered till the 14th day of life. Morphine sulfate was gradually stopped, reduced by 5 $\mu\text{g}/\text{kg}$ per day during a period of 8 days and withheld on the 22nd day after birth.

Case 1 has been followed for a period of 15 months. The signs of high-pitched cry, frequent irritability, and poor feeding leading to failure to thrive and developmental retardation were still observed at 6 months. Currently, the case has delays in developmental milestones, sitting alone at 1 year old, and not able to walk alone yet. Case 2 has been followed for 10 months. Her signs of high-pitched cry, frequent irritability, and poor feeding leading to failure to thrive continued in the follow-up period. She also experiences delay in the developmental milestone for rolling over alone at 9 months old. At discharge, Case 3 was found with excessive sucking and loose stool. At present, he has been followed up for 15 months, and delays in developmental milestones have been observed (sitting alone at 10 months old and not walking alone yet). Also, he manifests inappropriate laughing. Prolonged follow-up was recommended for further assessments on his neurobehavioral development.

3.2. Measurement outcomes

Urine specimens of the three neonates were first examined by an enzyme immunoassay to identify opiates, amphetamines, MDMA, marijuana, and ketamine, on the 1st day after birth. The positive specimens were tested by GC/MS to determine the presence of the targeted analytes above threshold concentrations. The results showed that none of the samples revealed a positive finding in urine, except Case 3, who was positive for morphine at a concentration of 308 ng/mL.

All quantitative analyses of hair specimens were performed with GC/MS in selected ion-monitoring mode with 20 ms of dwelling time for each ion (Figure 1). The GC/MS SIM chromatogram of the investigated drugs (HFBA, MA-HFBA, MOR-HFBA, MTD, EDDP, MOR-HFBA, COD-HFBA, and 6-AM-HFBA) after derivatization depicts pikes at 2.56 min, 3.06 min, 6.50 min, 7.13 min, 8.24 min, 8.42 min, and 8.83 min, respectively. Ions monitored in SIM mode were:

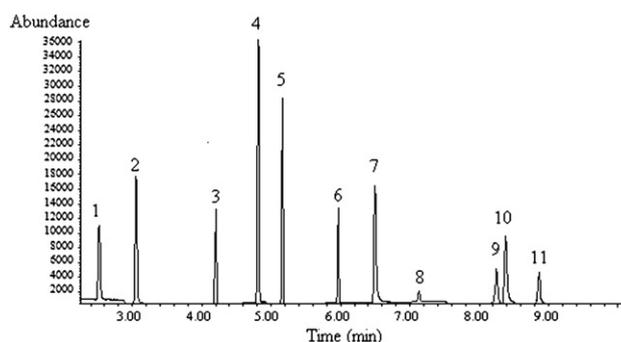


Figure 1 Gas chromatography/mass spectrometry-selected-ion monitoring (GC/MS-SIM) chromatograms of heptafluorobutyric acid anhydride (HFBA) derivatization of the investigated drug, which spiked with 5 ng/mg. The X-axis is intensity of quantification ions, and the Y-axis is the eluted time of the investigated drugs. 1 = amphetamine (AP); 2 = methamphetamine (MA); 3 = 3,4-methylene dioxymphetamine (MDA); 4 = 3,4-methylene dioxymphetamine (MDMA); 5 = norketamine (NK); 6 = ketamine (K); 7 = methadone (MTD); 8 = 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP); 9 = morphine (MOR); 10 = codeine (COD); 11 = 6-acetylmorphine (6-AM).

m/z 254, 210, 118 for MA; m/z 258, 123 for MA-d5; m/z 223, 294 for MTD; m/z 224, 297 for MTD-d3; m/z 262, 277 for EDDP; m/z 265, 280 for EDDP-d3; m/z 464, 677 for MOR; m/z 467, 680 for MOR-d3; m/z 464, 523, 411 for 6-AM; m/z 467, 526, for 6-AM-d3.

Hair samples of neonates 2–2.5 cm in length reflect the level of drug abuse of the mothers for 2–3 months before delivery. The results revealed positive readings for MA, MTD, EDDP, MOR, and COD at 865, 4145, 960, 180, and 180 pg/mg, respectively, for Case 1 (Figure 2A), and 1035, 15850, 1165, 1520, and 320 pg/mg, respectively, for Case 2 (Figure 2B). Figure 2C shows Case 3's AP, MA, MTD, MOR, COD, and 6-AM levels at 1115, 11396, 448, 3671, 1886, and 165 pg/mg, respectively.

4. Discussion

In the current study, we present neonatal case series whose mothers had heroin addiction with methadone replacement therapies during pregnancy for their clinical courses and treatment outcomes. To our knowledge, this is the first

report on this topic in East Asia.⁹ Two of the cases' mothers had no idea about using polydrug with amphetamine foisted. Mild to moderate NAS was identified among these cases, including moderate tremors when undisturbed, high-pitched cry, irritability, tachypnea, poor feeding with uncoordinated sucking for all of them, or even hypertonicity and cerebral dysfunction by electroencephalography for one case, which is similar to previous clinical reports.^{5–8} To a certain extent, findings on the scores of modified Finnegan neonatal abstinence scoring system might be a sign of the exposure levels and durations of heroin addiction reported by subjects. Fortunately, other than hepatitis C for one mother, the babies were born free of bloodborne virus infections and sexually transmitted diseases.³ Although all the cases were nearly full term (34–38 weeks), IUGR, defined by low birth weight, was observed in two cases (Table 1). Psychiatric comorbidity of the mothers and unconscious polydrug use make the clinical management even more challenging.^{8,9}

Quantitative hair specimens can be used to draw a gestational drug exposure profile and to study its potential link with the appearance of NAS. Nevertheless, the amount of neonatal hair is often insufficient because case mothers do not consent to infant hair collection for cosmetic or specific cultural reasons. Although the neonate hair sample is often small in amount, our modified assay method using 10 mg still provided enough sensitivity detection of the abused drugs, and gave applicable information to trace the illegal drugs used during pregnancy. The limit of detection and limit of quantification obtained were 40 pg/mg for AP, MA, MDA, MDMA, and MTD and 80 pg/mg for K, NK, EDDP, MOR, COD, and 6-AM when only 10 mg of hair sample was used.²⁰ Calibration curves for 10 analytes were established in the concentration range of 0.08–5 ng/mg with a correlation coefficient (r^2) of 0.997, using 200 pg/mg deuterated analogs of each analyte as internal standards for quantification.²⁰

In addition to patients' self reports, drug testing provides precise clinical information to assess individual exposures to illicit drugs. Samples of urine and blood are the most commonly used specimens, but their detection windows are only the preceding few days. Only one case's urine sample (Case 3) was found with traceable opiate because his mother used it 1 day before delivery. Because illicit drugs and their metabolites can disappear from the urine and the bloodstream within days, a neonatal hair specimen would be a better alternative because of its substantially wider detection window, enabling retrospective inspection of chronic exposure. In this study, we found that the mothers of Cases 1 and 2 both had experiences of methadone treatment programs because high concentrations of methadone and EDDP were found in neonatal hair. In addition, they also abused methamphetamine frequently. Moreover, the laboratory evidence showed that the mother of Case 2 abused heroin habitually, and Case 1 showed a low level of MOR and COD, indicating that the mother had abstained from heroin. Compared to Case 1, the higher levels of MTD and EDDP for Case 2 suggested that it could be the case that the illicit drugs she used contained methadone because she was only treated with methadone for 1 week. The other minor but noticeable issue was this case's weakened liver function due to

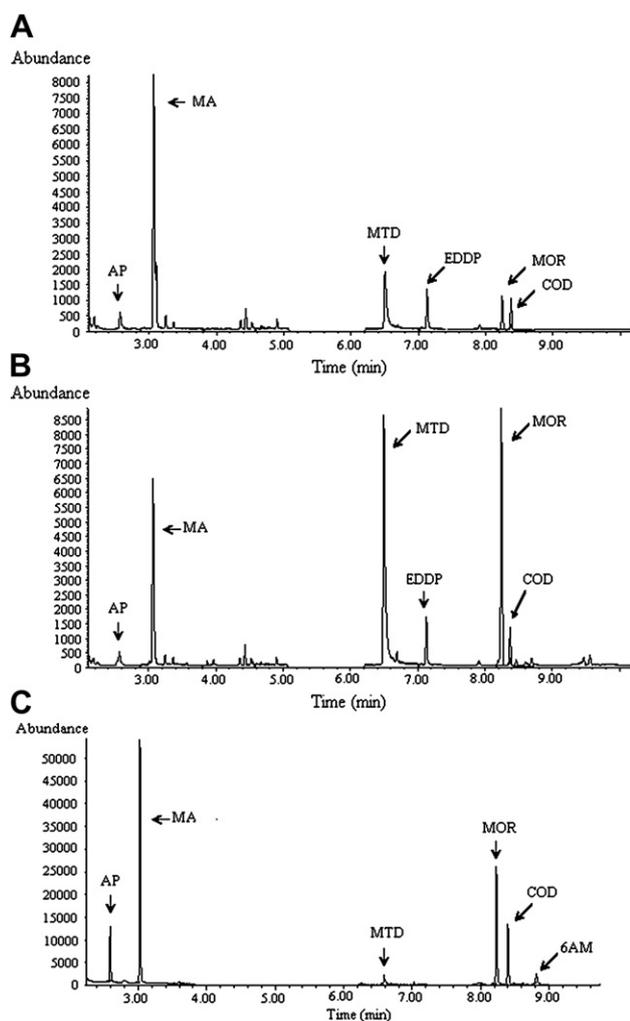


Figure 2 Gas chromatography/mass spectrometry-selected-ion monitoring (GC/MS-SIM) chromatogram of the neonatal hair of (A) Case 1, (B) Case 2, and (C) Case 3.

chronic hepatitis C infection, resulting in a prolonged half-life period of methadone, which is 24–36 hours for healthy people. Hair testing results of Case 3 showed that the mother abused both heroin and methamphetamine, and she had experienced fewer methadone treatments, shown by the low amount of methadone in her hair. Although amphetamine and/or methamphetamine was identified in neonatal hair samples in the current study, we did not find the related physical conditions or abnormal brain development suggested in the literature among these babies.^{23,24} However, concerns about neurobehavioral development for prenatal amphetamine exposure remain,²⁵ and further follow-up with intensive assessment is recommended. Drug abuse in women of childbearing age is an emerging issue worldwide.^{1,2} A better understanding on the clinical courses of subjects with polydrug use and experiences of treatment are in demand. Thus, the development of intensive prenatal care strategies and enrollment in treatment programs before/after delivery are of interest for future studies.

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