ORIGINAL ARTICLE

Methamphetamine detection in maternal and neonatal hair: implications for fetal safety

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Background: Methamphetamine misuse is a serious health problem of epidemic proportions. Use of this drug, particularly during pregnancy, is difficult to ascertain. Sparse information is available on gestational exposure.

Objectives: To quantify methamphetamine accumulation in hair, identify the use of methamphetamine with other drugs of abuse and characterise correlations between concentrations of methamphetamine in maternal and neonatal hair.

Subjects and methods: Motherisk laboratory at the Hospital for Sick Children routinely carries out analysis of methamphetamine in hair. Mothers and infants with positive results for methamphetamine in hair were identified. Drugs present in hair were analysed by ELISA and positive results were confirmed by gas chromatgraphy/mass spectrometry.

Results: 396 people positive for methamphetamine in their hair were identified from our database. Almost 85% of them were positive for at least one other drug of abuse, mostly cocaine. Eleven mother–baby pairs with hair positive for methamphetamine were identified. Methamphetamine levels in hair ranged between 0.13 and 51.97 ng/mg in the mothers and between 0 and 22.73 ng/mg in the neonates. Methamphetamine levels in mothers and neonates correlated significantly. One (9%) neonate was negative for methamphetamine even though the mother was positive.

Conclusion: To our knowledge, this is the first report on fetal exposure to methamphetamine during pregnancy, showing transplacental transfer of the drug, with accumulation in fetal hair. Hair measurement for methamphetamine in neonates is a useful screening method to detect intra-uterine exposure to the drug. The data also indicate that positive exposure to methamphetamine strongly suggests that the person is a polydrug user, which may have important implications for fetal safety.

Methamphetamine is a potent sympathomimetic drug that acts by inducing the release of biogenic amines in the brain, particularly norepinephrine and dopamine, leading to increased feelings of alertness, well-being, euphoria and exhilaration, as well as diminished appetite and increased sexual arousal.[1] At high doses, dopamine and serotonin release in the mid-brain may lead to hallucinations and even psychotic behaviour.[2]

Methamphetamine misuse as a recreational drug has been gathering momentum worldwide during the past two decades, with an estimated half a million people using this drug weekly in the US alone.[3] Methamphetamine is cheap and easy to produce in home laboratories, making it potentially easier to access than other substances of abuse.[4] Methamphetamine use has been linked to an increase in high-risk sexual behaviour, as well as myocardial infarctions, psychosis and aggressive behaviour.[1 5] Cocaine and methamphetamine have been shown to be the stimulant drugs of choice in North America, with methamphetamine rapidly becoming the preferred drug over cocaine in many parts of the world.[6–11] Young women in particular seem to prefer methamphetamine to cocaine and to use it more often than men.[7 12] It has been estimated that 5% of pregnancies are exposed to methamphetamine in North America.[13]

Methamphetamine has been shown to cross the placenta and affect the offspring of a variety of laboratory animals.[14–24] A major challenge in estimating maternal and fetal drug exposure is that a positive blood and urine test reflects only recent exposure. It is also more difficult to distinguish methamphetamine use from other drugs in urine samples, as many drugs are metabolised to methamphetamine.[25–27] Hair is an attractive matrix for screening for chronic drug exposure as it is easy to obtain, tends to grow predictably for long periods of time and can provide an estimation of the pattern of drug use if different sections of hair are studied. Scalp hair has been shown to reliably grow at a speed of around 1 cm/month.[27 28] As hair is produced in the hair follicle, it is exposed to the substances present in the blood at that time, trapping a small, but proportional, part of them. Hair does not easily lose the drugs that are caught in it, and bleaching or straightening by users does not preclude detection.[29] The temporal pattern of exposure can be defined if segmental analysis of the hair is carried out.

Methamphetamine use can be detected in hair, even after several years, if the section of the hair that grew during its use is still accessible.[30] The possibility of measuring drugs in neonatal hair has made the detection of human fetal exposure to methamphetamine during gestation possible, a subject on which sparse information exists.[31–36] Objective detection of fetal exposure to methamphetamine through hair analysis may allow prospective follow-up of this cohort to clarify the nature and magnitude of long-term adverse effects associated with this exposure.

The objectives of this study were threefold:

- to characterise methamphetamine accumulation in the hair of patients referred to our laboratory;
- to quantify exposure of methamphetamine with other drugs of abuse in this population; and
- to characterise correlations between maternal and fetal hair concentrations of methamphetamine in mother–baby pairs identified in our patient population.

Table 1 Statistical analysis of methamphetamine in hair

	n	Mean	−95% CI	95% CI	Median	Minimum	Maximum
Babies	20	3.01	0.598	5.42	0.92	0.18	22.73
Children	15	5.72	0.76	10.68	2.48	0.19	28.20
Adults	559	5.29	4.19	6.38	1.03	0.11	157.50

SUBJECTS AND METHODS

The Motherisk Laboratory at the Hospital for Sick Children in Toronto, Canada, routinely receives neonatal and adult hair samples for analysis from various hospitals throughout Canada. These include samples taken from neonates and their corresponding mothers.

On the basis of clinical suspicion of maternal drug misuse, the testing of hair was requested by either a doctor or the Children's Aid Societies, with the consent of the subjects or their legal guardians (in the case of children). The tested population included mostly women and their children, but some male adults were also tested, according to the needs of the Children's Aid Societies that refer the patients.

Hair samples were obtained preferably from the scalp, and the hair was cut as close to the skin as possible. The length of the sample obtained varied depending on the different characteristics of the hair in each patient (eg, length and type of hair).

Hair samples were analysed following previously well-described methods.[27 31] Briefly, hair was cut in 1–2 cm sections (representing a 1–2-month time period). Subsequently, 5–10 mg of hair was finely cut and incubated overnight at 52℃ in 1 ml methanol. The next day, methanol was pippetted and evaporated at 40℃ under a nitrogen stream. The sample was resuspended in 400 µl phosphate-buffered saline solution (pH 7.0). Individual drugs were analysed by ELISA, and positive results confirmed by gas chromatography/mass spectrometry.

Subjects who tested positive for methamphetamine in hair were identified from our laboratory database. These cases were mostly referred to the Motherisk Laboratory by Children's Aid Societies or by doctors suspecting drug abuse.

To compare exposure to other drugs of abuse between patients positive and negative for methamphetamine, we used the clinical results in the Motherisk database. χ^2 test was used to compare exposure patterns between patients positive and negative for methamphetamine.

We identified mother–child pairs who had positive results for methamphetamine in hair (in the mother, the child or both). Concentrations were compared using the Mann–Whitney U test and correlated using Spearman's rank test.

The study was approved by the ethics review board at the Hospital for Sick Children.

Table 2 Drug coexposure frequencies

No of different drugs found to test positive in hair of the same patient	Frequency (%) Methamphetamine positive	Frequency (%) Methamphetamine negative
1	18 (10.5)	653 (62)
2	60 (35.1)	270 (25.6)
3	56 (32.7)	100 (9.5)
4	20 (11.7)	20 (1.9)
5	13 (7.6)	9 (0.85)
6	4 (2.3)	1 (0.09)
Total	171 (100)	1053 (100)

RESULTS

Population characteristics

Between June 1997 and December 2005, our database accumulated results for 34 278 tests for drugs in hair, representing 8270 people. Almost 60% (4926) of these people were positive for at least one drug of abuse (12 962 positive tests).

We identified 396 people who were positive for methamphetamine in hair, accounting for 8% of the people with positive results in the database. The number of cases detected in our database increased sharply after 2005. The first cases of hair positive for methamphetamine in our database date from 2003 (six cases), followed by a slight increase in 2004 (eight cases) and a surge in 2005 (>300 cases). Preliminary data from 2006 suggest that this trend has not stopped.

The age distribution of this subgroup of patients positive for methamphetamine in hair was bimodal, with neonatal, paediatric and adult patients. Babies (defined for the purposes of our study as children <3 months of age; n = 19) had a mean (standard deviation (SD)) age of 2.1 (1.6) days and a median of 1.4 days. The children (>3 months but <16 years of age; n = 13) had a mean age of 3.9 (5.4) years and a median of 1.17 years. The adults (>16 years old; n = 247) had a mean age of 29.3 (8.7) years and a median of 29.3 years. There were 117 people classified as adults in the database for whom no exact age was available.

The median methamphetamine concentrations in the hair of babies (<3 months of age) was 0.92 ng/mg of hair. Children had a median methamphetamine concentration of 2.48 ng/mg of hair and adults had a median methamphetamine value of 1.03 ng/mg of hair (table 1). Data were not normally distributed (Shapiro–Wilks $p<0.01$ for all three groups). Concentrations in the three groups (babies, children and adults) were not significantly different from each other (Kruskal–Wallis analysis of variance test $p = 0.67$), suggesting that there are no marked age-dependent variations in the metabolism of methamphetamine (table 1).

Among subjects positive for methamphetamine whose hair was also tested for other drugs of abuse (n = 171), 83.5% were positive for at least one other drug, of which the most common was cocaine (table 2). This is in contrast with the sample of people who had a negative result for methamphetamine, but were positive for other drugs in hair (n = 1053). In this group only 38% of the patients were positive for more than one drug (χ^2 $p<0.001$). In the sample of subjects with hair positive for methamphetamine, cocaine was the most commonly coused drug (65% of patients positive for methamphetamine had a positive cocaine result), followed by cannabis (37.6%) and opiates (30.2%). Patients were tested for at least four different drugs.

Taking into account missing results (ie patients positive for methamphetamine for whom other drugs were not tested), the lowest percentage of coexposure (−95% confidence interval (CI) with all missing results considered to be negative) for cocaine was 60%, cannabis 22% and opioids 16%. Thus, even in the unlikely scenario that all patients not tested for cocaine were actually negative, the lowest rate of coexposure for methamphetamine and cocaine in our sample would be 54% (table 3). Most commonly observed drug combinations in

Table 3 Coexposure to other drugs in patients positive for methamphetamine in hair

	Total neg	Total pos	Total missing result	Total	% pos/ pos+neg	% pos/tot	95% CI (pos/pos+neg)	95% CI for (pos/total)
Cocaine	126	234	36	396	65	58.8	60 to 69.6	54 to 64
Cannabis	146	88	162	396	37.6	22.2	32.8 to 42.6	18.2 to 26.6
Opiates	148	64	184	396	30.19	16.16	24.1 to 36.8	12.6 to 20

neg, negative; pos, positive; tot, total.

patients positive for methamphetamine were cocaine–methamphetamine (20%), cocaine–methamphetamine–cannabis (9.5%) and cocaine–methamphetamine–opiate (7.6%).

Maternal–neonatal correlations

Eleven mother–baby pairs with hair positive for methamphetamine were identified, out of a sample of 396 subjects positive for methamphetamine. Median methamphetamine values in the hair of this subset of patients were 1.75 ng/mg of hair in the mothers (range 0.13–51.97) and 1.63 ng/mg in the neonates (range 0–22.73; table 4). No difference was found between methamphetamine concentrations in babies and their mothers (Mann–Whitney U test, $p = 0.97$), suggesting that the transplacental transfer of methamphetamine is extensive. Maternal and neonatal hair methamphetamine levels correlated significantly (Spearman's $r = 0.8$, $p = 0.003$; fig 1).

None of the pairs identified included mothers with negative results, but there was one (9%) neonate who had a negative methamphetamine result even though the mother tested positive. Therefore, the sensitivity of our test to detect maternal use of methamphetamine using neonatal hair was 91.6% (95% CI 58.7% to 99.7%). In contrast, positive maternal hair had a 100% (95% CI 69% to 100%) sensitivity in detecting positive neonatal hair (ie, all babies testing positive for methamphetamine in hair had mothers who tested positive for methamphetamine in hair).

DISCUSSION

Drugs of abuse have been tested in hair since the early 1950s, and techniques have advanced considerably in the past 20 years.[29] In adults, scalp hair has been shown to grow at a mean rate of about 1 cm/month.[27 28] As the hair is produced in the hair follicle, it is exposed to the substances present in the blood at that time, trapping a small, but proportional, fraction of them. Hair does not easily lose the drugs that are trapped in it, and bleaching or straightening by users does not affect detection.[29] The results of hair testing can yield a quantitative estimate of intensity of use of particular drugs over defined periods of time.[27 37]

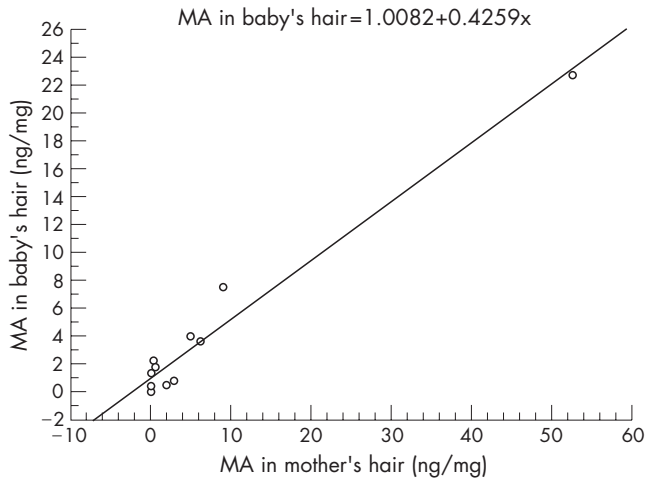

Figure 1 Correlation between maternal and neonatal methamphetamine (MA) concentrations in hair. Spearman's $r = 0.8$; $p = 0.003$.

Hair is being increasingly used by child protection services to screen care givers of children living with suspected drug users.[38] This has most certainly provided marked benefits not only for children at risk but also for families with care givers incorrectly suspected of drug misuse.[27]

Fetal hair begins to form at the end of the second trimester (around 20 weeks of gestation)[39] and shares with adult hair the ability to retain drugs present in the fetal circulation, thus allowing the evaluation of fetal exposure to drugs of abuse during the second part of the pregnancy.[31] Fetal hair can be easily obtained from the neonate up to several months after birth, permitting a wider window of detection of intrauterine exposure.

The detection of drugs in neonatal hair has also allowed confirmation of transplacental transfer of several drugs of abuse in humans, a process previously substantiated only in animal experiments.

The typical age for methamphetamine misuse encompasses women's reproductive age, suggesting that the risk of fetal exposure to this drug may be high. The recent stimulant drugs of choice in North America have been shown to be cocaine and methamphetamine.[6] Drug misusers who are pregnant tend to have poor access to healthcare and are often reluctant to disclose their addiction owing to the fear of stigmatisation and legal consequences, including the removal of the infant from home. It has been estimated that only a small proportion of drug addicts who are pregnant register for prenatal care before the last trimester,[6] and that <25% of cases of drug exposure during pregnancy are disclosed by the mothers.[40] Obstetrical complications, including miscarriage, placental insufficiency, fetal death and sexually transmitted diseases, are common among mothers who misuse drugs.[6] Also, children exposed to drugs of abuse during pregnancy exhibit a threefold higher prevalence of major medical problems than children not exposed to them.[6] Mothers who misuse drugs during pregnancy are likely to continue to do so in subsequent pregnancies.

Studies in pregnant animals have shown that methamphetamine crosses the placenta into the fetus rapidly and extensively after intravenous administration to the mother.[14 19 41] Tissue analysis of fetal ewes the mothers of which had received a methamphetamine dose similar to that used in humans showed accumulation of the drug in tissues, the brain in particular, to levels several-fold higher than the fetal plasma concentrations.[14] Similar observations have been made in postmortem studies of newborns perinatally exposed to methamphetamine.[42–44] Also, fetal exposure to methamphetamine has been suggested by studies evaluating the presence of amphetamines in meconium and cord blood samples.[45]

The consequences of fetal exposure to methamphetamine are still unclear, but a variety of short-term and long-term adverse effects have been suggested. Animal experiments have shown inconclusive results on the issue of fetal malformations, with some, but not all, animal models showing varying degrees of teratogenicity.[14–16 19–21 24] Most studies assessing the consequences of methamphetamine exposure during pregnancy have been criticised because of methodological problems, in particular the

Table 4 Statistical description of methamphetamine values in hair of babies and mothers

	n	Mean	−95% CI	95% CI	Median	Minimum	Maximum
Mothers' MA concentrations in hair	11	6.99	−3.2	17.2	1.75	0.13	51.97
Babies' MA concentrations in hair	11	3.98	−0.43	8.4	1.63	0	22.73

MA, methamphetamine.

difficulties in identifying methamphetamine exposure status and small sample sizes.[13]

In a longitudinal study of 65 Swedish children exposed in utero to methamphetamine, reduced weight, height and head circumference were observed up to 4 years of age compared with unexposed Swedish children born in the same year.[46–48] Also, at 14 years of age, the children exposed in utero to methamphetamine had an intellectual performance significantly below their classmates.[47] Collectively, these findings suggest that children exposed in utero to methamphetamine are at risk of developmental problems, because of either the effect of direct exposure to the drug during pregnancy or growing in the environment associated with parental methamphetamine misuse, or probably both. Similar findings have been published in other parts of the world.[5 7 11 49 50]

Our study provides several new findings in understanding the reproductive toxicology of methamphetamine.

Firstly, we have shown that, unlike misusers of other drugs, methamphetamine misusers almost invariably tend to coutilise other drugs. This has to be borne in mind when attempting to attribute adverse developmental effects to methamphetamine alone, as coexposure to other drugs should be accounted for as a potential confounder.[49] Epidemiologically, hair positive for methamphetamine in our study sample has a 90% predictive value for at least one more drug of abuse, making it a powerful biological marker of complex addiction and possibly higher perinatal risk.

To our knowledge, this is the first evidence of the transplacental transfer of methamphetamine in humans as evidenced by accumulation in fetal hair, with accumulation in babies' hair at levels similar to those of the mothers. This finding has several important implications. It provides a basis for the development of a screening test in high-risk cases, which could eventually lead to better neonatal monitoring and protection of babies at risk. Because neonatal hair grows in the last trimester of pregnancy, a positive hair test for methamphetamine in the baby is a biomarker of maternal addiction, as the mother has long known she is pregnant by the seventh month of pregnancy. It also suggests that fetal exposure to the drug is extensive and that neonatal hair testing could be a useful method to monitor for effects of exposure to methamphetamine during pregnancy. The positive correlation of methamphetamine in the hair of mothers and babies also provides a potential means to quantitatively estimate fetal exposure, as maternal reports are not likely to be accurate. Unfortunately, given the retrospective and anonymous nature of the study, no clinical data are available for the babies identified as positive for methamphetamine. We acknowledge and truly regret this pitfall, but we expect that our results showing the potential of hair testing to detect neonatal exposure to methamphetamine will allow us and others to identify and prospectively follow exposed babies.

In summary, measurements of methamphetamine in maternal and neonatal hair shed light on a new epidemic of substance abuse by pregnant women. Studies correlating methamphetamine exposure with pregnancy outcome are needed and are amply justified in the light of our results.

What is already known on this topic

- Methamphetamine is rapidly becoming the stimulant drug of choice in many parts of the world. The usual age of misuse, encompassing women's most fertile years, has led to an increasing number of prenatal exposures to this drug.
- The consequences of fetal exposure to methamphetamine are not clear and, even though many observational studies suggest an increased risk of a wide range of developmental effects, few large studies have been conducted to date. Human placental transfer of the drug into the fetal compartment has been suggested by anecdotal reports (forensic case studies and meconium and cord blood studies), but no systematic study has been conducted to date.

What this study adds

- Evidence pointing to placental transfer of methamphetamine leading to fetal systemic exposure is presented.
- The detection of methamphetamine in the hair of neonates can enable easy systematic detection of prenatal exposure to methamphetamine, which in turn will permit identification and prospective follow-up of cohorts of exposed patients. This will allow clarification of congenital effects of the drug. Also, hair detection provides the opportunity to carry out protracted detection of neonates exposed in utero, something that other matrices such as meconium and blood do not allow.

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