

Detection of illicit drugs in meconium to assess neonatal abstinence syndrome (NAS)

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Abstract

Aim: Consumption of drugs of abuse during pregnancy bears a high risk for the well-being development of the fetus. Since the neonatal abstinence syndrome (NAS) develops hours to days after birth, pediatricians are challenged for adequate therapy. Meconium is the ideal matrix for identification of drug consumption in the 2nd and 3rd trimester of pregnancy. Drugs of abuse (DOA) consumption during pregnancy bears a high risk for the health development of the fetus. Since the neonatal abstinence syndrome (NAS) develops hours to days after birth, pediatricians are challenged with adequate therapy. In Germany, the amount of opiate addicted individuals was estimated to be 200.000, according to the *Drug dependence report* 2011 [1]. Almost 25% of those are women at the childbearing age. In the Charité, the largest hospital in Berlin, in 60 out of 3500 deliveries (1,7%), the mother was involved in illicit drug consumption in 2011 [2]. The analytical challenge is a fast and reliable LCMSMS procedure for drugs of abuse testing in meconium.

Methods: Methanolic extraction of meconium and detection of drugs of abuse in a 2 step solid phase extraction procedure using a single LCMSMS run.

Results: From the 121 cases analyzed, 52 meconium samples were positive for the following substances: methadone (16), opiates (9), cannabis (10), buprenorphine and amphetamine (2). Combined positive findings were obtained for methadone and opiates (8), cocaine and opiates (2). Methadone, amphetamine and cannabis were identified in 1 sample.

Conclusion: In case of psychophysical abnormalities of the newborn, appropriate therapy can be started prior to the onset of the withdrawal symptoms if the drug consumed during pregnancy has been correctly identified.

1. Introduction

Human pregnancy consists of three trimesters, the first being critical for the neuro-development of the fetus, the second for the formation of the skeleton, eyes and the sense of hearing, and the third for the development of the organism and the function of the organs (e.g. liver; kidney). Meconium is the sum of concentrated bile, vernix caseosa, swallowed skin cells, lanugo hair and epithelial cells from amniotic fluid stored in the neonates' inoperable bowel. It is excreted 24 to 48 hours after birth and represents the ideal matrix for the pediatrician to screen for maternal drug of abuse consumption from the second trimester on. The process of fetal development and the onset for meconium formation is shown in figure 1.

In pregnancy, fetal neuronal alterations via the placental pathway are effective nearly simultaneously to drug consumption. As fetal metabolism is not yet effective, the fetus is exposed to the psychoactive substances in a prolonged and in a much more potent manner.

Neurodevelopmental damages to the fetus have been reported for the consumption of alcohol and neurostimulants. No severe teratogenic effects have been observed with the consumption of opiates (Tab. 1).

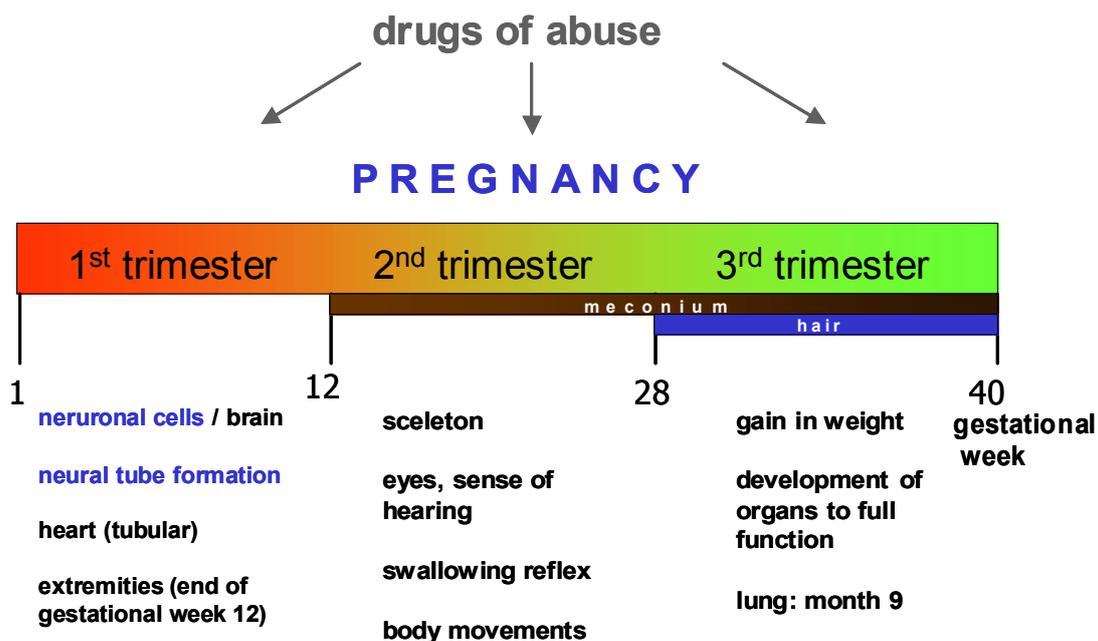


Fig. 1. Fetal development during pregnancy.

Pregnant women in maintenance programs with methadone or buprenorphine have to be substituted sufficiently to avoid life threatening opiate withdrawal symptoms in utero and further additional drug consumption to improve health and social status of the expectant mother.

Tab. 1. Possible fetal malformations by drugs of abuse.

| | Drug | Teratogenicity |
|---------------------|----------------------------|---|
| Neuronal damage | alcohol | yes - heart (90%) - hearing (30%) - mental development |
| | amphetamin and derivatives | yes - neuronal development - musculo-skeletal anomalies (talipes) |
| | cocaine | yes - microcephalus - heart dysplasia |
| Withdrawal symptoms | morphine | no |
| | methadone | no |
| | buprenorphine | ? |
| | cannabis | no |

In 70-90% of the newborn disjunction from maternal circulation at birth will lead to a neonatal abstinence syndrome (NAS) within the following days of its life [3]. The newborn will show tremor, irritability, sweating, insomnia, and excessive high pitched crying over hours. Non nutritive sucking requires intensive medical treatment and intravenous feeding. However, no information about maternal drug of abuse disposition is known when newborns are dropped off in a baby hatch.

Analytical procedures must detect the most abundant drugs of abuse for legal as well as for medical purposes. LCMSMS is the gold standard to fulfill this task, because in most cases only a small amount of meconium is available. However, the aim is a sensitive detection of the drug(s) rather than a quantification.

2. Material and Methods

Meconium samples were extracted with methanol and adjusted to pH 6.0 with phosphate buffer. After solid phase extraction, in a first step the cannabis metabolite THCCOOH is eluted from the SPE and evaporated to dryness. Into the same vial a second elution step is performed for stimulants, opiates and opioides. After solvent evaporation analytes are resuspended in HPLC-buffer (0,1% aqueous formic acid / 0,1% formic acid in acetonitrile) and analyzed by tandem mass spectrometry on a API 4000 system (AB SCIEX) with positive electrospray ionization in the Multiple Reaction Monitoring mode (MRM).

3. Results and Discussion

The limits of detection of the LCMSMS procedure were determined according to DIN 32646 (Tab. 2). During 2009 to March 2013 our laboratory received a total of 121 meconium specimens to analyze for drugs of abuse (Fig. 2). A number of 52 cases was tested positive for the following substances: methadone (16), opiates (9), cannabis (10), buprenorphine and amphetamine (2). Combined positive findings were obtained for methadone and opiates (8), cocaine and opiates (2). Methadone, amphetamine and cannabis were identified in 1 sample. The most recent case from March 2013 was positive for methadone, morphine and cannabis.

Tab. 2. Limit of detection (LOD) in meconium specimen.

| Substance | LODs in Meconium (ng/g) |
|------------------|-------------------------|
| amphetamin | 1,5 |
| metamphetamin | 1,3 |
| MDA | 0,7 |
| MDMA | 1,9 |
| MDEA | 1,5 |
| cocaine | 0,7 |
| benzoylecgonine | 1,2 |
| THCCOOH | 0,9 |
| morphine | 1,1 |
| methadone | 1,4 |
| EDDP | 0,8 |
| buprenorphine | 0,4 |
| norbuprenorphine | 0,3 |

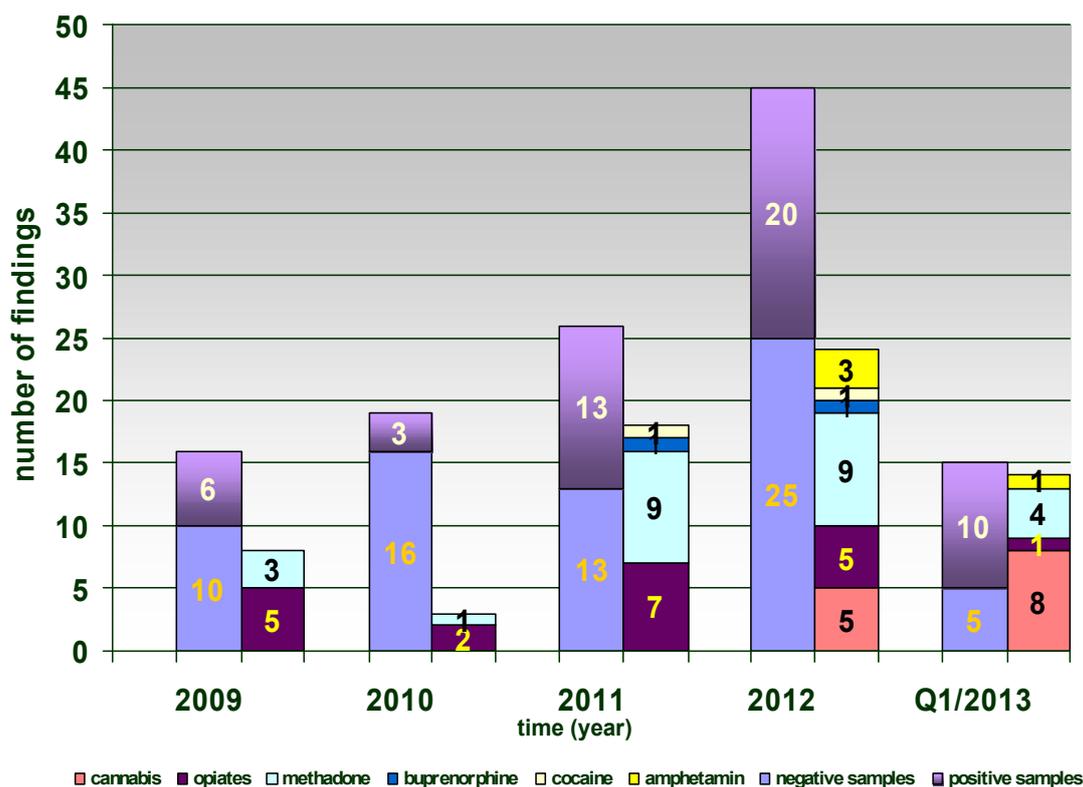


Fig. 2. Detected drugs of abuse in meconium specimen from 01/2008 to 03/2013.

4. Conclusions

Psychophisic abnormalities of the newborn caused by drug exposure to stimulants during pregnancy require immediate treatment after correct identification of the drug. On the contrary, withdrawal symptoms due to opiate consumption or methadone therapy appear within hours to days, often leading to NAS. They can be treated promisingly. However, in all cases coconsumption of illicit drugs must be excluded to check for the compliance of the mother. With this fast and reliable LCMSMS-based drug screening procedure, neonatologists can now recommend revocation of parental care by the authorities in case of drugs of abuse consumption short after delivery. Changes in German legislation in January 2012 “Bundeskinderschutzgesetz“ now enable neonatologists to indicate maternal drug consumption to the authorities in cases of health risks for the newborn. Meanwhile the effectiveness of the federal law for child protection mentioned above nearly doubled the orders to analyze meconium for drugs of abuse with a further increase to be expected in 2013.

5. References

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