

Detection of drugs in paired maternal and umbilical cord blood samples

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Abstract: Objectives. The consumption of drugs during pregnancy or delivery leads to pre and intranatal drug exposure of the fetus. The purpose of this study was to examine paired blood samples of the mother and the umbilical cord regarding drug distribution.

Methods. Over a period of two years, 22 pregnant women with known or admitted drug use were selected. Paired blood samples of the mothers and the umbilical cord blood were collected shortly before and during birth/caesarean section, respectively. The samples were subjected to systematic immunochemical, HPLC-DAD, GC/MS and LC-MS/MS analysis and compared regarding presence of drugs.

Results. Methadone, THC-COOH, tramadol, benzoylcegonine, citalopram, carbamazepine, lamotrigine, perazine, methylphenidate, quetiapine, ranitidine and most constituents of spinal and epidural anaesthesia were found in both, maternal and umbilical cord blood samples. THC, 11-OH-THC, olanzapine, diphenhydramine and telmisartan were found in maternal blood only.

Conclusions. As previously shown a variety of drugs is able to pass the placenta of pregnant woman. Umbilical cord blood appears to be a viable matrix for the detection of maternal drug consumption. Drugs administered during labour and birth could be detected in umbilical cord blood. Further studies with a greater collective of women with known drug use including analyses of fetal/infant samples will yield additional information in the future.

Key Words: umbilical cord, placental transfer, forensics, legal medicine, maternal drug abuse.

INTRODUCTION

Maternal consumption of pharmaceuticals during pregnancy is a frequent and common matter. In this context, in-utero drug exposure due to abuse of pharmaceuticals or the use of illicit drugs is a widespread problem [1]. The exposure of the developing fetus or the newborn infant to these drugs is influenced by the placental permeability for a specific substance (concentration gradient (dose administered to the mother), physical and chemical properties of drug molecules), the metabolism of the substances, active transport mechanisms, etc. [2-9]. The mechanisms of placental transport are well described elsewhere [2-9], although when dealing with inexplicable drug exposure of infants or newborn babies

in for instance forensic or criminal proceedings, it raises the question whether the substance was administered directly or ingested via placental transfer. Against this background the present study aimed to analyse and compare paired blood samples collected from pregnant women with known medication or admitted drug abuse. Samples were collected before or shortly after birth and from their umbilical cord during birth, in order to examine which drugs are actually detectable in umbilical cord blood and whether drugs administered during labour and/or delivery reach the unborn child. These findings might provide information supporting the interpretation of for instance toxicological findings in forensics (window of detection and degree of exposure).

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METHODS

Over a period of two years we collected 22 blood samples from pregnant women and the umbilical cord vein of their newborns. Blood samples from the mothers were taken before or shortly after birth, but on the day of delivery. Umbilical cord blood samples were taken during birth.

The following information were captured: Date and time of birth, Caesarean section (yes/no), withdrawal symptoms (yes/no), age of mother, duration of pregnancy, medication (current and during pregnancy), use of illicit drugs, alcohol consumption and drug use / abuse prior to pregnancy.

Plasma samples were screened by immunochemical analysis for cannabinoids, opiates, cocaine metabolites, benzodiazepines, methadone, amphetamine, synthetic designer drugs, tricyclic antidepressants and admitted drug intake. Further screening and validation of achieved data was performed using GC-MS, HPLC-DAD and / or LC-MS/MS.

Immunochemical analysis

Immunochemical analyses were performed using the fully automated Olympus AU400 Chemistry Analyzer and 200 µL serum in case of cannabinoids, opiates, cocaine metabolites, benzodiazepines, methadone and tricyclic antidepressants. Screening for amphetamines and methamphetamines was performed using the Alere Microplate Kit for amphetamines and methamphetamines. When necessary, samples were precipitated with 2 mL acetone.

Gas chromatography–mass spectrometry (GC-MS)

Depending on the analyte 0,5 - 1 mL serum was extracted using solid phase (SPE) or liquid-liquid extraction. In case of SPE elution was performed using methanol and/or dichloromethane/iso-propanol/NH₃ (80:20:4; v:v:v). After evaporation to dryness derivatization was achieved by adding either acetic anhydride/pyridine (screening), or acetic anhydride/ perfluoropropionic anhydride (PFPA; cocaine and opiates), or methyl-bis-heptafluor(o)butyramide (MBHFBA) or N-Methyl-N-

(trimethylsilyl)trifluoroacetamide (MSTFA)/ ethyl acetate (cannabinoids) and incubation in 100°C for 30 minutes. Extracts were then resuspended in 70 µL ethyl acetate.

High-Performance Liquid Chromatography with Diode-Array Detection (HPLC-DAD)

One mL serum was buffered with 3 mL phosphate buffer pH 6 (screening) or pH 9 (benzodiazepines) and extracted using 1-chlorbutane/ isopropanol (9:1) (screening) or dichloromethane/ isopropanol (9:1) (benzodiazepines) liquid-liquid extraction. Samples were then evaporated to dryness and resuspended with 70 µL acetonitrile.

Liquid chromatography– tandem mass spectrometry (LC-MS/MS)

Fifty µL serum were mixed with 150 µL methanol. The mixture was filtered using a cellulose acetate filter and used for analysis.

RESULTS

Admitted or known intake of drugs during pregnancy

Out of 22 women in the study collective, four were known to be substituted with methadone. Five women took the antiepileptic lamotrigine during pregnancy. Two women took citalopram, one perazine, one olanzapine, one carbamazepine, one quetiapine and two methylphenidate. Two women did not provide any information (Fig. 1 A). One woman admitted the use of cocaine four days prior to delivery.

Medication during birth

Four women in the study collective got an epidural anaesthesia during birth, three women a spinal anaesthesia and one was known to be treated with fentanyl. In 14 cases no information regarding medication prior to or during birth was available (Fig. 1 B).

Methadone

Seven out of 22 women were substituted with methadone. In all seven cases methadone as

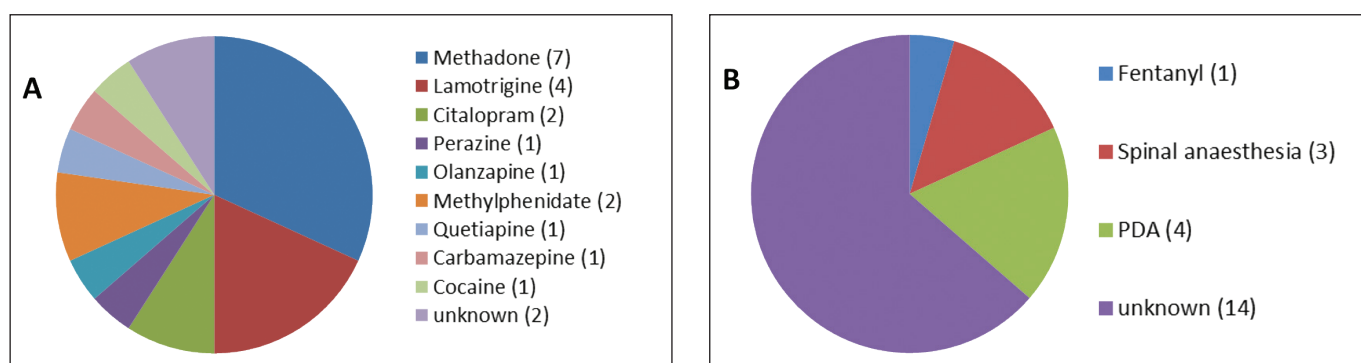
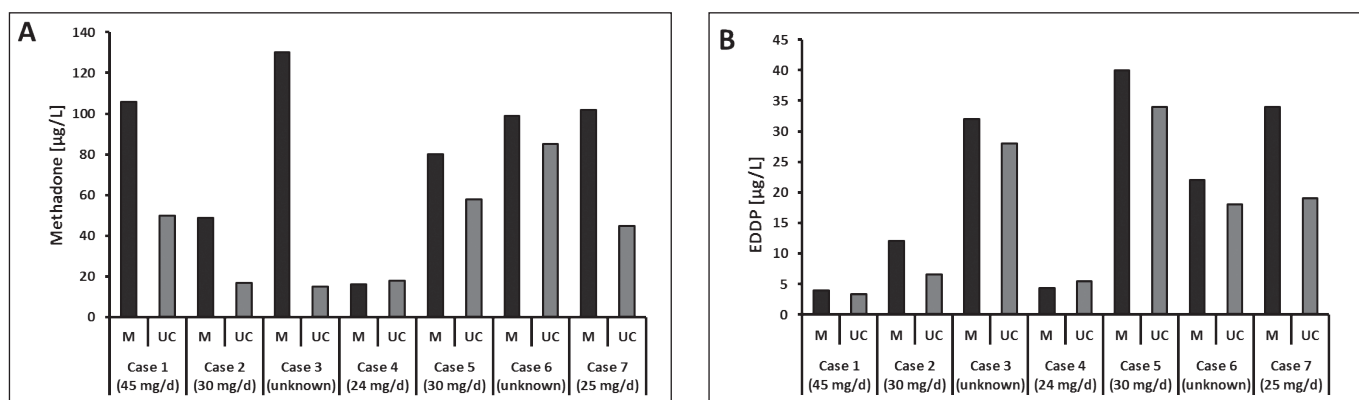


Figure 1. Overview of the indicated drug consumption by the 22 participants of the study (A) and of the pharmaceuticals administered before and during delivery / caesarean section (B). () = number of cases.

Table 1. Overview of the qualitatively detected substances in maternal (mother) and umbilical cord (UC) plasma

		Detected Substances	Drugs prior/during delivery
Case 1	Mother	Ranitidine, Norfentanyl	Fentanyl: 0,2 ml
	UC	Ranitidine, Norfentanyl	
Case 2	Mother	Bupivacaine, Diphenhydramine, Ranitidine	Spinal anaesthesia
	UC	Bupivacaine	
Case 3	Mother	Bupivacaine	Spinal anaesthesia
	UC	Ranitidine	
Case 4	Mother	Perazine	Taxilan (Perazine): 25 mg, 1-0-0
	UC	Perazine	
Case 5	Mother	Norfentanyl, Ropivacaine, Lidocaine, Meptazinol	Epidural anaesthesia
	UC	Norfentanyl, Ropivacaine, Lidocaine, Meptazinol	
Case 6	Mother	Olanzapine, Mepivacaine, Bupivacaine	Epidural anaesthesia, Zyprexa (Olanzapine) 10 mg: 0-0-1
	UC	Mepivacaine	
Case 7	Mother	Methylphenidate, Telmisartan	unknown
	UC	Methylphenidate	
Case 8	Mother	Methylphenidate, Quetiapine	Seroquel (Quetiapine)
	UC	Methylphenidate, Quetiapine	
Case 9	Mother	Methylecgonine, Benzoylcgonine	Cocaine 4 days before delivery (see also figure 3 C)
	UC	Methylecgonine, Benzoylcgonine	

**Figure 2.** Concentration of methadone (A) and EDDP (B) in maternal (M) and umbilical cord (UC) plasma. d = day.

well as the metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) was found in the blood taken from the umbilical cord (Fig. 2). The average concentration of methadone in the maternal plasma exceeded the concentration in the umbilical cord by factor 1.9 ± 0.37 . In the available seven dyads the pattern appeared to be independent of the daily methadone dose. In one case (Case 4) methadone and EDDP concentration in the umbilical cord plasma exceeded the concentrations in the maternal plasma.

Lamotrigine

Four women indicated regular taking of lamotrigine. However, the substance could only be detected in two out of four cases. In these two cases maternal and umbilical cord plasma concentrations correlated with the indicated daily intake (Fig. 3 A). The lamotrigine maternal/umbilical cord serum concentration ratios were 1.27 (Case 1) and 1.16 (Case 2).

Tramadol

In one dyad, we were able to detect tramadol in maternal and umbilical cord plasma (Fig. 3 B). The tramadol levels in both samples were almost equal (4.0

µg/L in maternal plasma; 4.7 µg/L in umbilical cord plasma).

Cocaine

In one case, the mother admitted the use of cocaine four days prior to delivery. We found benzoylcgonine, traces of methylecgonine but no cocaine in maternal and umbilical cord plasma (Fig. 3 C and Table 1 (Case 9)). In this one case benzoylcgonine levels in umbilical cord plasma were higher than in maternal plasma.

Cannabinoids

Two of the women who were known to be substituted with methadone were positive for cannabinoids as well. Tetrahydrocannabinol (THC) as well as the metabolites THC-COOH und 11-OH-THC were detected in maternal plasma. In contrast, only THC-COOH was detected in the umbilical cord plasma (Fig. 4).

Citalopram

Citalopram was found in maternal and umbilical cord plasma in one case (Fig. 3 D). Citalopram levels were similar.

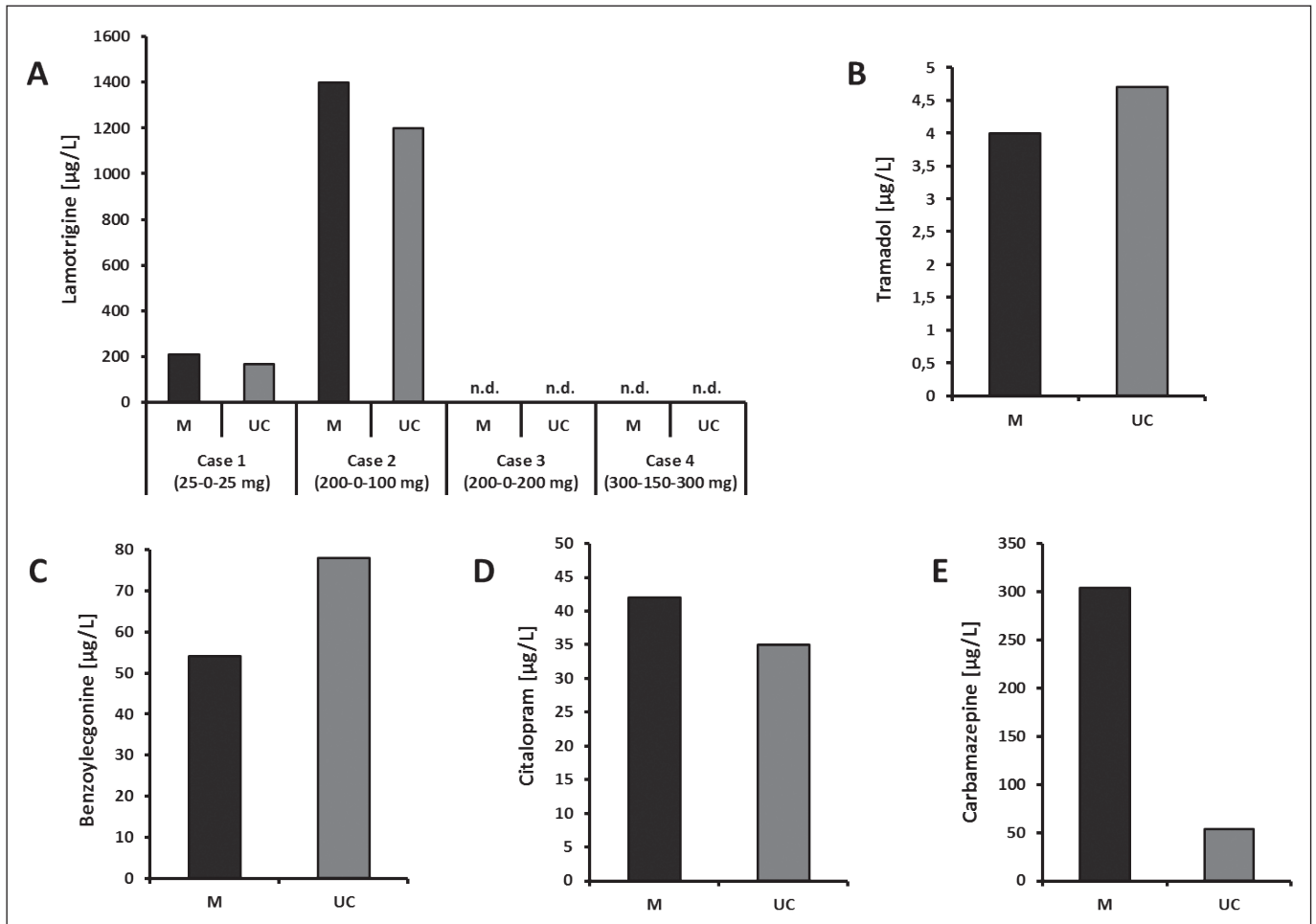


Figure 3. Concentration of lamotrigine (A), tramadol (B), benzoylecgonine (C), citalopram (D) and carbamazepine (E) in maternal (M) and umbilical cord (UC) plasma. n. d. = not detected.

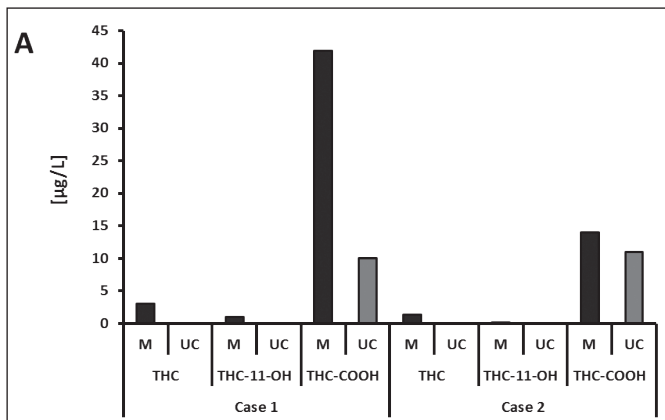


Figure 4. Concentration of cannabinoids in maternal (M) and umbilical cord (UC) plasma. THC = Tetrahydrocannabinol; THC-11-OH = 11-Hydroxy- Δ^9 -THC; THC-COOH = 11-Nor-9-carboxy- Δ^9 -THC.

Carbamazepine

In one case, carbamazepine could be detected in maternal and umbilical cord plasma (Fig. 3 E). Carbamazepine concentrations were higher in maternal plasma.

Epidural and spinal anaesthesia

Since the constituents of the epidural and

spinal anaesthesia (bupivacain, ropivacaine, lidocaine, mepivacaine, meptazinol and fentanyl) and their concentrations were known, we did not aim to quantify the detected substances. Bupivacaine, ropivacaine, lidocaine, mepivacaine, fentanyl and meptazinol could be detected in maternal and umbilical cord plasma (Table 1). However, this was not true for all deliveries where those substances were administered.

Miscellaneous

In the present case of olanzapine intake, the substance could only be detected in maternal plasma. Perazine, quetiapine and methylphenidate were found in maternal and umbilical cord plasma (Table 1). In one case diphenhydramine was found in maternal plasma, but could not be detected in the associated umbilical cord. The same was true for telmisartan. Ranitidine was detected in the maternal and umbilical cord plasma (Table 1).

DISCUSSION

As shown previously [10-14], methadone and EDDP in utero exposure can be determined in the umbilical cord blood. While average methadone

concentrations were higher in maternal blood, average EDDP concentrations were almost similar. This observation appeared not to depend on the daily methadone intake. The ability of methadone to pass the placenta, the determination of methadone and its glucuronide conjugates in maternal and umbilical cord plasma and the neonatal outcomes of methadone consumption during pregnancy have been extensively discussed elsewhere [1, 10-14] and are not subject of this study. Based on the limited number of samples, our findings are in accordance to the previous observations. However, methadone and EDDP concentrations in maternal and umbilical cord plasma did not seem to correlate with the admitted daily methadone intake. This observation might be attributed to individual variations in dose and rate of metabolism, time of intake and possible parallel consumption.

Regarding teratogenic effects of methadone use/abuse during pregnancy, a decrease in mean birth weight, a smaller head circumference and birth length, pre-term birth and neonatal abstinence syndrome (NAS) have been described [15, 16].

The lamotrigine maternal and umbilical cord plasma levels were almost similar. These findings are in line with previous observations where the lamotrigine infant/maternal serum concentration ratio ranged in monotherapy from 0.40 to 1.38 (median 0.91) and lamotrigine levels in serum correlated strongly with the lamotrigine levels in cord blood [17, 18]. The current literature indicates no difference in the overall malformation rate between the children exposed to lamotrigine and any type of control group [19].

Like morphine [20], tramadol is a lipophilic compound which can readily cross the human placenta [21, 22]. Although tramadol was detected in one dyad only, our findings also indicate that tramadol possesses a distinct placental permeability with similar tramadol levels in maternal and umbilical cord plasma. Teratogenic effects of tramadol have been described, but the risk increase appeared to be moderate [23].

Cocaine has been reported to pass the human placenta [11]. However, in a case of admitted cocaine consumption four days prior to delivery, we were only able to detect benzoylecgonine and traces of methylecgonine in paired maternal and umbilical cord plasma. Benzoylecgonine levels in the umbilical cord were higher than in the paired maternal plasma. The lack of cocaine detection can probably be attributed to the time span between cocaine intake and sampling as well as the fast metabolism of cocaine. The link between cocaine use during pregnancy and teratogenicity is mainly based on case reports. The described teratogenic effects include limb reduction, genitourinary tract malformations, cleft palate, congenital cardiovascular malformations, developmental delay and direct effects of cocaine on cortical neurodevelopment [24-31].

Antidepressants and their metabolites were shown to be detectable in umbilical cord samples. In comparison with fluoxetine, paroxetine and sertraline, citalopram showed the highest ratio of cord to maternal serum concentrations suggesting an efficient placental transfer [32-34]. However, umbilical cord levels of citalopram were almost invariably lower than corresponding maternal levels. These findings are supported by our observation. Citalopram was detected in paired maternal and umbilical cord plasma, with a slightly higher concentration in maternal plasma. To our knowledge, there is no significant association of citalopram with congenital malformation.

Even though our results indicate a placental transfer of carbamazepine, maternal plasma levels exceeded umbilical cord concentrations by far. While based only on one mother/umbilical cord pair, this observation might be misleading. Regarding carbamazepine, it has recently been shown that even carbamazepine in drinking water and at typical environmental concentrations is transmitted from mother to embryo [35]. In the underlying case, date and dose of carbamazepine intake were not known, but based on the findings published by Kaushik and colleagues [35] a higher transfer ratio can probably be expected. Children exposed to carbamazepine in utero were shown to have an increased risk of having a major malformation like oro-facial malformations and neural tube malformations [19].

In the two cases of cannabinoid consumption during pregnancy, only the metabolite THC-COOH was found in umbilical cord blood plasma, while THC, 11-OH-THC and THC-COOH was detected in maternal plasma. Due to their lipophilic nature cannabinoids are able to cross the placental barrier [36]. In Rhesus monkeys THC was detectable in fetal plasma 15 min after infusion of the mother and fetal THC plasma concentrations equilibrated to maternal concentrations within 3 h [37]. Also THC, 11-OH-THC and THC-COOH were shown to be detectable in meconium, clearly demonstrating the placental permeability [38].

In the two cases on hand, the form of consumption, the date of intake and the consumed amount were not known. The absence of THC and 11-OH-THC in umbilical cord plasma in the present study might be attributed to low maternal THC and 11-OH-THC plasma levels in the umbilical cord. Antenatal use of cannabinoids has been associated with long-term effects like inattention, impulsivity, deficits in problem-solving that require sustained attention and visual memory, analysis and integration, increased errors of omission and academic underachievement in the spelling and reading areas [39-45]. Although teratogenic effects of cannabis in human have been described [46-48], most literature suggests lack of or modest teratogenicity.

All detectable constituents of the epidural

and spinal anaesthesia administered during labour (bupivacain, ropivacaine, lidocaine, meptazinol and fentanyl) were found in umbilical cord plasma. As previously shown, this suggests a fast and significant placental transfer of these substances during labour [49-62].

Olanzapine could only be detected in maternal plasma but has been described to readily cross the human placenta in a normal-term placenta perfused single cotyledon system [63]. The lack of olanzapine detection might be attributed to a problem with sample preparation or very low concentrations in the umbilical cord plasma. In line with previous studies, we were also able to detect a substantial placental transfer of ranitidine [54] and perazine. Time and amount of intake were not known. The current literature suggests no associations of H(2)-blockers was with perinatal mortality, premature delivery, low birth weight, low Apgar scores and other major teratogenic risk of malformations [64-67]. To our knowledge, there are no studies available regarding possible teratogenic effects of perazine.

Recently, Peters and colleagues showed that methylphenidate crosses the placenta of mice and reaches measurable concentrations in fetal brain [68]. In our study we were able to show, that methylphenidate passes the human placenta as well. Although further studies and quantitative measurements are needed, the potential risk of fetal methylphenidate exposure should be considered. In 1993 Debooy and colleagues described prematurity, growth retardation, and signs of neonatal withdrawal after intravenous methylphenidate abuse during pregnancy, but no particular teratogenic anomaly or severe developmental delay [69]. Apart from that, possible teratogenic effects of methylphenidate have recently only been addressed in rats, rabbits and mice [70-72].

Furthermore diphenhydramine and telmisartan were detected in maternal plasma. To our knowledge the placental transfer of diphenhydramine has only been studied in sheep and rats [73-76]. At least in sheep, rapid and extensive placental transfer of diphenhydramine after maternal drug administration has been shown [73-75]. In contrast, we were not able to detect diphenhydramine in the umbilical cord plasma. However, again dose and time of intake were unknown. Thus further testing will be necessary in order to investigate the placental permeability of diphenhydramine in humans. Same is probably true for telmisartan. According to the current literature telmisartan has fetal toxic effects with neonatal acute renal failure and/or renal impairment [77, 78]. Yet there is no information available on placental permeability of telmisartan in humans.

This study aimed to begin the compilation of an overview on the ability of pharmaceuticals and illicit drugs to cross the barrier of the human placenta and on their traceability. Although some of the findings are only based on single observations, these data can be of significant help when examining drug exposure of infants or newborn babies in forensic or criminal proceedings. In addition many of the substances which are able to cross the human placental barrier were shown to be teratogenic. Thus, not only the elucidation of for instance an inexplicable drug exposure in infants or newborns, but also possible links between antenatal drug exposure and neurological consequences, long-term effects and a toxic influence on brain maturation can be addressed.

Undoubtedly, further research will be necessary in order to create a bigger database with statistically significant data.

Conflict of interest. The authors declare that there is no conflict of interest.

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