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## Drug testing in biological samples vs. maternal surveys for the detection of substance use during whole pregnancy

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### ABSTRACT

**Background:** Early diagnosis of nicotine, ethanol and drug use during pregnancy is critical in order to provide adequate care. Current screening procedures show limitations in terms of reliability and short windows of detection.

**Objectives:** To investigate the prevalence and identify biomarkers of substance use and changes in substance use during pregnancy. To compare drug testing results in different types of biological samples (maternal hair, meconium, placenta, umbilical-cord) with self-reported data.

**Participants and setting:** Prospective cohort study using data from pregnant women and their newborns.

**Methods:** Biological matrices were collected at birth and analyzed by liquid chromatography tandem mass spectrometry. A paper survey was provided to determine substance use habits.

**Results:** 867 mother-newborn pairs were included. According to the analysis of biological samples, 29.1% cases were positive for one or more substances (13.6% nicotine, 8.4% ethanol, 8.3% cocaine, 6.4% cannabis, 5.7% opioids). The profile of the substance-using mother was a single woman, <28 years-old, with no higher education and unemployed. Segmental maternal hair analysis showed a decrease in tobacco, cannabis and cocaine use throughout pregnancy ( $p < 0.001$ ). The level of concordance between results from interviews and from biological analyses was weak for opioids, cocaine, and cannabis (kappa coefficient  $< 0.40$ ). Maternal hair detected the highest number of cases, followed by meconium and by placenta and/or umbilical-cord.

**Conclusions:** Maternal survey was not a reliable screening technique. Analysis of maternal hair detected the highest number of cases with the broadest detection window (whole pregnancy).

### KEYWORDS

Drug; newborn; intrauterine exposure; meconium; placenta

### Introduction

Substance use by pregnant women is associated with increased morbidity and mortality during both the perinatal period and the subsequent development of the child.<sup>1-4</sup>

The incidence of their teratogenic effects is highest during the first trimester, but other effects (somatometric development, respiratory, neurological problems, etc.) may not become

evident until several years later, even when the child was asymptomatic as a newborn.<sup>3,5</sup>

The identification of pregnant women that consume illegal substances has become difficult in recent years. The main reason is the change in the type of substances used; heroin use has declined significantly and the consumption of drugs such as cannabis and cocaine has increased.<sup>6,7</sup>

Prevalence data of substance use among pregnant women are scarce. In the United States the reported rates of consumption of substances among pregnant women were 11.5% for ethanol, 14.7% for nicotine and 8.5% for illicit drugs, while these rates among non-pregnant women corresponded to 54.5% for ethanol, 20.8% for nicotine and 14% for illicit drugs.<sup>8</sup> By comparison, in Spain, the prevalence of licit and illicit drugs, was 71.3% for ethanol, 28.4% for nicotine, 9.8% for cannabis, and 1.2% for cocaine among women aged 15–44 years.<sup>9</sup>

At present, the most common methods used to detect cases of substance use during pregnancy are maternal interview or survey. These methods have proved to be associated with a low reliability and a high percentage of underdiagnosis.<sup>4</sup> Mothers often provide inaccurate answers for fear of legal and/or social repercussions, because of the scarce awareness that socially accepted substances (ethanol/nicotine) can cause problems in the fetus, because of their own feelings of guilt or because of biases in their memory. The habit can be easy to hide due to the unrecognizable abstinence syndrome caused by substances such as cannabis or cocaine.<sup>4,10–13</sup> Also, how the interview is performed and by whom has a significant impact on the mothers' answers.<sup>14</sup>

The diagnosis of substance use during pregnancy can be reached in an objective manner by analyzing biological matrices from the newborn (meconium, neonatal hair or urine), from the mother (plasma, urine, hair, breast milk, saliva or sweat),<sup>4,15,16</sup> or from the mother/newborn pair (placenta, umbilical-cord or amniotic fluid). Each matrix offers advantages and limitations.<sup>4</sup> The most frequently employed matrices are both mothers' and newborns' urine and, in some cases, the newborns' meconium. The main limitation of urine is the short window of detection (several days). In the case of meconium, the biological sample may not be available at delivery due to pass before birth. Hair analysis offers the longest window of detection. Hair grows at an average growth rate of 1 cm/month, and the segmental hair analysis provides a chronological picture of substance use during the different trimesters of pregnancy; however, this matrix has not been frequently employed for evaluating drug use during

gestation. Placenta and umbilical-cord are emerging as alternative matrices to meconium.

The analysis of biological samples also has caveats and limitations. Positive results may be due to passive exposure, ingestion of products contaminated by the substance, or consumption of prescription drugs containing or metabolizing to such substance.<sup>3</sup>

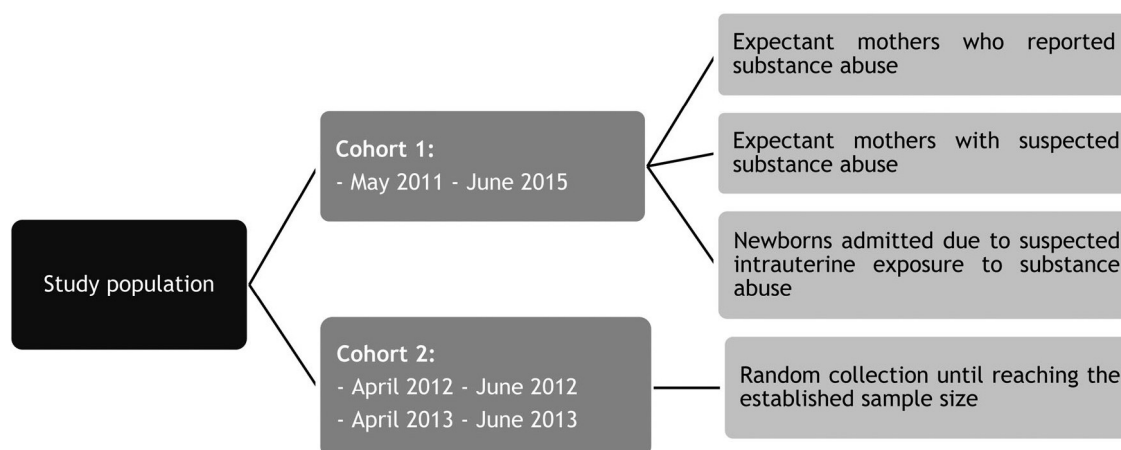
The objectives of this study were to investigate the prevalence and identify biomarkers of substance use and changes in substance use during pregnancy, as well as to compare drug testing results in different types of biological samples (maternal hair, meconium, placenta, umbilical-cord) with self-reported data. An early diagnosis is key to enable interventions that help the mother, and to monitor the degree of exposure of the fetus, in order to minimize the eventual appearance of short and long-term pathologies.

## Methods

### Participants

This was a prospective cohort study comprised by women who gave birth (and their newborns) during the study period 2011–2015 in two level III hospitals (>3000 deliveries/year). This included all live neonates born during the study period, and their mothers, regardless of gestational age or method of delivery. Participants were not included in the study if any of the biological matrices (hair, meconium, placenta or umbilical cord) was not collected, or if the mother suffered any psychiatric or neurological disorder. The outline of the study cohorts is described in [Figure 1](#). All participants authorized the collection of their samples and filled a survey after signing a declaration of informed consent. The study was approved by the Galician Clinical Research Ethics Committee (Code number 2011/203).

All participating women were asked to complete a survey after delivery covering epidemiological aspects (age, level of education, profession, and marital status), obstetric information (previous pregnancies, miscarriages, and premature deliveries), substance use habits before and



**Figure 1.** Outline of the study cohorts.

during pregnancy and the substance use habits of their babies' fathers.

Biological matrices collected for the analysis included maternal hair, meconium, placenta and umbilical cord. Maternal hair was stored inside an envelope at room temperature until analysis. Meconium, umbilical cord and placenta were stored in polypropylene containers at  $-20^{\circ}\text{C}$  until analysis. The biological matrices were analyzed once for each participant. Each maternal hair sample, if enough amount of hair was available, was divided into 3 segments corresponding to the 3 trimesters of pregnancy and analyzed.

#### **Analysis of biological matrices**

The analyses of maternal hair, meconium, umbilical-cord and placenta were performed by the Toxicology Laboratory at the University of Santiago de Compostela, following previously published and validated procedures.<sup>17-21</sup> Liquid chromatography tandem mass spectrometry (LC-MS/MS) was used as the confirmation and quantification technique. Cocaine, opioids and amphetamines were analyzed in all the biological samples (hair, meconium, umbilical-cord and placenta); nicotine only in hair; ethanol only in meconium; and cannabis in hair and meconium.

Hair and meconium samples were used as biological matrices of reference.<sup>4</sup> Samples of placenta and umbilical cord were only analyzed if a positive result was obtained in either maternal hair or meconium. Whenever possible, the strand of hair was divided into three segments corresponding to the three trimesters of pregnancy (2 cm

segment for the 3<sup>rd</sup> trimester, and 3 cm segments for the 2<sup>nd</sup> and 1<sup>st</sup> trimester). If not enough amount of hair was available, a strand of 8 cm was analyzed.

#### **Statistical analysis**

The data analysis was carried out jointly with the Methodology and Statistics Unit of the hospital. The full cohort was used to analyze consumption frequencies and to compare the different matrices. Analyses of sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio were performed to study the validity of three matrices (meconium, placenta, and umbilical-cord) for the detection of opioids and cocaine. Positive results of hair segment corresponding to 3<sup>rd</sup> trimester of pregnancy as were used as reference results.

A nested case-control study was designed for the initial cohort. A case was considered when a positive result was found in any of the matrices analyzed, and a control was considered when the results of the analyses of all matrices were negative and the mothers reported no substance use during their pregnancy. The kappa coefficient was used to analyze the concordance between the substance use reported by the participants in the survey and the results of the analyses of the matrices. The chi-squared test was used to determine which variables were statistically associated with events of substance use during pregnancy (cases). The variables for which statistical

**Table 1.** Positive results (n) to different substances in each biological matrix.

	Hair					Meconium	Placenta	Umbilical-cord	Total n (%)*
	T3	T2	T1	SU	Total				
Nicotine	60	65	64	49	116	NA	NA	NA	116 (13.6)
Ethanol	NA	NA	NA	NA	NA	59	NA	NA	59 (8.4)
Cannabis	17	19	28	20	49	22	NA	NA	56 (6.4)
Cocaine	23	35	35	30	70	15	8	8	72 (8.3)
Amphetamines	1	1	7	9	17	1	0	0	18 (2)
Opioids	11	18	17	13	36	27	22	23	50 (5.7)**

NA: Not analyzed; T3: hair segment third trimester; T2: hair segment second trimester; T1: hair segment first trimester; SU: single hair segment (entire pregnancy).

\* The % refers to the total number of samples analyzed for each substance.

\*\* Seven cases who used morphine as an analgesic during the peripartum period had positive results in their meconium, placenta, and umbilical-cord samples but negative ones in their hair samples.

significance was found were included in a multivariate logistic regression model.

The McNemar test was used to analyze the evolution of the substance use report during pregnancy. The Wilcoxon's signed Rank test was used in those cases in which the hair strand could be segmented in order to study whether the consumption had decreased between the 1<sup>st</sup> and the 3<sup>rd</sup> trimester of pregnancy.

A *p* value of less than 0.05 was considered to be significant. Statistical software programs SPSS® (IBM SPSS Statistics for Windows, version 19.0) and Epidat 3.1 were used for the statistical analyses.

## Results

### Participants

A total of 867 mother-newborn pairs were included in the study. Of these, a total of 858 samples of hair, 752 samples of meconium, 142 samples of placenta, and 140 samples of umbilical-cord were analyzed. 83% of the women participating in the study responded to the survey.

### Prevalence of substance use based on survey and drug testing results

Forty-nine per cent of the participants endorsed that they had consumed substances before becoming pregnant, 19.7% acknowledged that they had consumed substances during their pregnancy, and 16% did not respond. Among the women who recognized drug use before pregnancy, 50.2% reported ethanol use, 32.6% nicotine, 9.6% cannabis, 3.7% cocaine, 0.9% heroin and 0.4% amphetamines. Among the women who

admitted substance use during pregnancy, 10.7% reported ethanol use, 15% nicotine, 2.1% cannabis, 0.8% cocaine, and 0.2% heroin. When asked about their partners' substance use habits, 34.8% of the women reported that their babies' fathers consumed one or more substances, with ethanol and nicotine being the most prevalent.

The analysis of the different biological matrices collected yielded a positive result in at least one of the matrices studied for at least one of the substances analyzed in 253/867, 29.1% of the participants; 13.6% were positive for nicotine, 8.4% ethanol, 6.4% cannabis, 8.3% cocaine and 3.8% heroin and methadone (Table 1).

### Risk profile of women who use any substances during their pregnancies

The study population was comprised by a control group of 306 mother-newborn pairs and a case group of 246 pairs. The demographic and socioeconomic characteristics of the participants and the results of their univariate comparison are shown in Table 2. A multivariate logistic regression analysis was performed to assess the influence of the patients' socioeconomic aspects on their consumption of substances. The risk factors for substance use during pregnancy included no higher education with an odds ratio (OR) of 2.15 (95% confidence interval [CI]: 1.33-3.46), unemployment with an OR of 1.79 (95% CI: 1.13-2.81) and being single or divorced with an OR of 1.89 (95% CI: 1.06-3.37). Older age proved to be a protective factor against substance use with an OR of 0.95 (95% CI: 0.91-0.99).

**Drug use changes throughout the pregnancy**

We analyzed whether the women changed their consumption habits during their pregnancy based on surveys and on hair testing (Table 3). The survey was completed by 100% of the controls and 81% of the cases. The results of the comparative analysis revealed that the knowledge of conception significantly reduced the women's

**Table 2.** Demographic and socioeconomic characteristics of the participants divided into cases and controls. Comparative analysis using the chi-squared test or Fisher's exact test.

	Controls n (%)	Cases n (%)	p value
Mother's age (n = 552)			<i>p</i> < 0.001
<28 years	40 (13.1)	69 (28)	
29-38 years	236 (77.1)	154 (62.6)	
>38 years	30 (9.8)	23 (9.3)	
Level of education (n = 430)			<i>p</i> < 0.001
University	125 (47.5)	39 (23.4)	
Non-university	138 (52.5)	128 (76.6)	
Employed (n = 472)			<i>p</i> < 0.001
Unemployed	65 (23.6)	83 (42.1)	
Paid employment	210 (76.4)	114 (57.9)	
Marital status (n = 411)			<i>p</i> < 0.004
Single/divorced	30 (12)	38 (23.6)	
Married/in a common-law relationship	220 (88)	123 (76.4)	

consumption of nicotine, ethanol, cannabis, cocaine, and opioids (*p* < 0.05).

In the case group (n = 246), an analysis of the maternal hair segmented by trimesters of pregnancy was carried out (n = 179 participants), enabling us to study whether the consumption actually decreased throughout the pregnancy. A log-rank test revealed a decrease of exposure throughout pregnancy to nicotine (n = 65, *p* < 0.001), cannabis (n = 29, *p* < 0.001), cocaine in those cases in which it was not consumed together with ethanol (n = 39, *p* < 0.001), and opioids (n = 23, *p* = 0.043). It is important to highlight that among the participants that consumed cocaine and ethanol (cocaehtylene detected in hair), no reduction of drug use during pregnancy was observed. No reduction was observed either in the case of amphetamines or methadone.

**Drug testing vs. maternal survey**

The degree of concordance between the survey responses and the results of the analyses of hair

**Table 3.** Substance use prior to and during the pregnancy based on self-report (survey).

		Use prior to the pregnancy		Use during the pregnancy	
		Control, n (%)	Case, n (%)	Control, n (%)	Case, n (%)
Some degree of substance abuse	Yes	134 (43.8)	158 (55.6)	0	94 (33.1)
	No	172 (56.2)	73 (25.7)	306 (100)	136 (47.9)
	DK/NR	0	53 (18.7)	0	54 (19)
Nicotine	Consumption	70 (22.9)	123 (43.4)	0	85 (29.9)
	<10 cig./day	47 (15.4)	61 (21.5)	0	70 (24.6)
	10-20 cig./day	20 (6.5)	55 (19.4)	0	14 (4.9)
	>20 cig./day	3 (1)	7 (2.5)	0	1 (0.4)
	NR	1 (0.3)	56 (19.7)	0	55 (19.4)
Ethanol	Consumption	168 (54.9)	132 (46.5)	0	34 (12.1)
	Sporadic	149 (48.7)	93 (32.7)	0	32 (11.3)
	During weekends	19 (6.2)	36 (12.7)	0	1 (0.4)
	Daily	0	3 (1.1)	0	1 (0.4)
Cannabis	NR	0	55 (19.4)	0	55 (19.4)
	Consumption	17 (5.6)	46 (16.2)	0	14 (4.9)
	Sporadic	17 (5.6)	33 (11.6)	0	10 (3.5)
	During weekends	0	2 (0.7)	0	0
Cocaine	Daily	0	11 (3.9)	0	4 (1.4)
	NR	1 (0.3)	58 (20.4)	0	58 (20.4)
	Consumption	4 (1.3)	20 (7.1)	0	7 (2.5)
	Sporadic	4 (1.3)	13 (4.6)	0	6 (2.1)
Heroin	During weekends	0	7 (2.5)	0	1 (0.4)
	Daily	0	0	0	0
	NR	1 (0.3)	54 (19)	0	54 (19)
	Consumption	0	8 (2.9)	0	2 (0.7)
Methadone	Sporadic	0	3 (1.1)	0	0
	During weekends	0	0	0	0
	Daily	0	5 (1.8)	0	2 (0.7)
	NR	1 (0.3)	54 (19)	0	54 (19)
Methadone	Consumption	0	9 (3.2)	0	9 (3.2)
	No consumption	305 (99.7)	221 (77.8)	306 (100)	221 (77.8)
	NR	1 (0.3)	54 (19)	0	54 (19)

NR: no response.

**Table 4.** Sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio of the meconium, placenta, and umbilical-cord matrices, using hair corresponding to the 3<sup>rd</sup> trimester as reference matrix.

	OPIOIDS			COCAINE		
	Meconium	Placenta	Umbilical-cord	Meconium	Placenta	Umbilical-cord
S	90.9%	81.8%	81.8%	28.5%	22.2%	22.2%
SP	97.6%	89.8%	87.1%	99.5%	100%	100%
PPV	50%	52.9%	47.3%	66.6%	100%	100%
NPV	99.7%	97.2%	97.1%	97.5%	82.2%	82%
PLR	37.6	8.08	6.3	57.5	–	–
NLR	0.09	0.2	0.2	0.7	0.7	0.7

S: sensitivity, SP: specificity, PPV: positive predictive value, NPV: negative predictive value, PLR: positive likelihood ratio, NLR: negative likelihood ratio.

and/or meconium samples was calculated. A kappa coefficient  $< 0.40$  was found for opioids (heroin and methadone), cocaine, and cannabis. This reflected a weak or poor concordance between self-report and drug detection in hair and/or meconium, indicating under-reporting for these substances. A kappa coefficient of 0.660 was obtained for nicotine, thus proving a good correlation between the participants' self-reported consumption and that detected in hair. A poor concordance was found for ethanol self-report and meconium analysis (kappa coefficient  $< 0.40$ ); but in this case, self-report detected a higher number of cases than meconium analysis.

### Comparison of the biological samples

The different biological matrices (meconium, placenta and umbilical-cord) were compared to maternal hair (3<sup>rd</sup> trimester segment) to establish their diagnostic performance for opioids and cocaine consumption during pregnancy. In the case of opioids, test sensitivity was 90.9% in meconium, 81.8% in both, placenta and umbilical-cord, and specificity was 97.6% in meconium, 89.8% in placenta and 87.1% in umbilical-cord. In the case of cocaine, test sensitivity was 28.5% for meconium, 22.2% in both, placenta and umbilical-cord, and specificity was 99.5% in meconium, and 100% in placenta and umbilical-cord (Table 4).

### Discussion

Following current clinical guidelines, the analysis of biological matrices is reserved for those situations in which the consumption of substances is explicitly reported and/or suspected during the perinatal period. The detection of these cases is rare and leads to underdiagnosis.<sup>10,11,22</sup>

Maternal interview is associated with underreporting of substance use.<sup>12</sup> In our study, the percentages of substance use detected by means of the completion of the survey were 15% for nicotine, 10.7% ethanol, 2.2% cannabis, 0.8% cocaine, 0.2% heroin, and 1% methadone, while the analytical results were 13.6% nicotine, 8.4% ethanol, 6.4% cannabis, 8.3% cocaine, and 3.8% heroin and methadone. We found under-report of cocaine, cannabis and opioids (kappa coefficient  $< 0.4$ ). A good concordance was found in the case of nicotine (kappa coefficient = 0.66), which may be attributed to the legal status of nicotine. In the case of ethanol, the participants' self-reported consumption was greater than the consumption confirmed by biological analyses, probably because only meconium and not hair could be tested for the ethanol biomarker (ethyl-glucuronide).

The data from our study revealed a higher percentage of illicit drug use than previously published reports. This percentage was even higher than the one reported in studies with non-pregnant women performed during the same time period in our community.<sup>23</sup> We detected a lower number of positive results for heroin (2.4%) and a greater number for cocaine (8.3%), probably related to changes in the consumption habits in that period of time.

There is limited data about drug use during pregnancy based on analysis of biological samples. In 1999, Sherwood *et al.*<sup>24</sup> performed a random urine analysis on samples from 807 pregnant women from South London and found that approximately 16% of the study population had consumed illicit drugs, a similar percentage to that found in our cases (16.8%). A similar study performed in Barcelona (Spain) between 2002 and 2004<sup>25</sup> reported positive results for illicit drug use in 10.9% of their study population. The use of meconium as the single matrix could explain the lower prevalence.<sup>4,17,18,26</sup> Other studies analyzed

meconium and maternal hair (3<sup>rd</sup> trimester) and obtained positive results in 15.9% of samples,<sup>10</sup> despite only 1.9% of the expectant mothers acknowledging consumption; these results are similar to ours. By contrast, other studies<sup>22</sup> obtained fewer positive results for cocaine in hair (2.6%). Our strength compared to them is the use of a segmented hair analysis that also allowed us to analyze substance use during the 1<sup>st</sup> and 2<sup>nd</sup> trimesters of pregnancy.

Hair analysis detected the highest number of cases and showed the broadest window of detection, followed by meconium. The possibility of using placenta and umbilical-cord samples was evaluated as an alternative to meconium. Taking maternal hair as a reference matrix, the three samples yielded a specificity >87% for cocaine and opioids. The three matrices were sensitive for opioids (81.8-90.9%), however the sensitivity for cocaine was <29%. Comparing meconium, placenta and umbilical cord, meconium was 10% more sensitive than both placenta and umbilical cord, a finding that coincides with data previously published by members of our group.<sup>17,27,28</sup>

The overall profile of the substance-using mother in this study was that of single women, under the age of 28, with no higher education and unemployed. An association with the mothers' age, professional skills or level of education has not been clearly established.<sup>10,22</sup>

The greater diagnostic yield of the biological methods raises the question of implementing frequent drug screening among pregnant women in order to detect the habit as soon as possible to effectively intervene and protect the mothers' and the children's health. Some authors claim that such screening would not be feasible or cost-effective.<sup>3,29</sup> However, based on our results, its implementation will depend on the prevalence of drug use among pregnant women in a community and the available resources. Prevalence rates such as those outlined in our study justify an increase of screening frequency using biological samples.

### Conclusion


Current protocols used to identify substance use among pregnant woman lead to underdiagnosis. In this study, we identified a greater reluctance of the

mothers to self-report their use of illegal drugs. The use of several diagnostic matrices allowed us to analyze consumption habits throughout the entire pregnancy. Hair analysis detected the highest number of cases, and it showed the broadest window of detection, followed by meconium.

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