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# Infants born to women with substance use: Exploring early neurobehavior with the Dubowitz neurological examination

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## ABSTRACT

**Background:** There is a special concern regarding substance using pregnant women due to the possible adverse effects on the infant. While the immediate effects of prenatal substance exposure are well known, the long-term data on the infants' neurodevelopment is inconclusive.

**Aims:** The purpose of this study was to assess early neurobehavior of infants of mothers with substance use using the Dubowitz examination and to follow their neuromotor development until one year of age.

**Study design and subjects:** Ninety-five pregnant women with a recent history of substance use were recruited and followed up at the maternity outpatient clinic. Follow-up data was collected from hospital records and maternal interviews. The Dubowitz neurological examination was performed to the 54 clinically healthy term infants. The results were converted into optimality scores and compared to normative values from clinically healthy term infants derived from a separate normative population. The infant's neuromotor development was followed up to one year of age.

**Results:** Only 7% of the infants born to women with recent or current substance use reached optimal scores (< 30.5) in the Dubowitz neurological examination compared to 95% reported in normative population. Sixty-three percent of the newborns needed follow-up based on physiotherapeutic assessment of neurobehavior. By 12 months of age, the neuromotor status of 88% (n = 30) of these infants was found normal.

**Conclusions:** A high percentage of infants of mothers who were referred prenatally to hospital due to substance use showed suboptimal neurological findings during their first days of life.

## 1. Introduction

The prevalence of substance use during pregnancy is concerning: in the United States 9.3% of pregnant women self-reported current alcohol consumption and 5.3% illicit drug use [1]. In addition, an immense increase in the use of prescription opioids among fertile and pregnant women has been reported in many countries [2].

There is a special concern for these mothers, as the substances cross through the placenta potentially impairing fetal growth and development. Findings in the neonates exposed to substances vary from severe withdrawal symptoms requiring immediate treatment to more subtle changes such as poorer muscle tone and irritability [3]. Substance use frequently co-occurs with several other risk factors for perinatal development, such as insufficient maternal care, poor nutrition and overall health. Therefore, it is hard to isolate the effects of substances

per se on the developmental outcome [4,5]. The high prevalence of polydrug use further complicates the situation [6]. The effect of intrauterine drug exposure on fetal neurodevelopment is inconclusive. A recent study found that children exposed antenatally to methadone had poorer inhibitory control and difficulties in sustaining their attention [7]. In contrast the study by Kaltenbach et al. (2018) found children exposed prenatally to opioids to show normal development in early childhood. Detection of the infants at risk of poor developmental outcome enables to focus support and early interventions to risk families and thus alleviate possible developmental deficits [8].

The NICU Neurobehavioral Scale (NNNS) has been designed to evaluate the neurobehavioral status of neonates exposed to substances in utero [9,10]. Studies using NNNS have shown changes in the neurobehavior of infants exposed to substances during pregnancy and identified infants with high- and low-risk for abnormal

**Abbreviations:** Dubowitz, The Dubowitz neurological examination; NNNS, The NICU Neurobehavioral Scale; EuroASI, European Addiction Severity Index

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neurodevelopment [11]. Compared with NNNS, the Dubowitz neurological examination is faster and simpler to complete as the interrater reliability is above 96% even with inexperienced staff [12]. It is a validated method for the neurological evaluation of newborn infants consisting of carefully selected series of neurological and neurobehavioral items encompassing various aspects of neurological functions [12]. The Dubowitz has been widely studied in different at-risk infant populations, but not in a population of infants of poly substance using mothers [13,14].

In this study, the aim was to observe the early neurological state and neuromotor development of infants born to women with substance use using the Dubowitz. It was hypothesized that these neonates present with abnormal outcomes in the Dubowitz.

## 2. Materials and methods

### 2.1. Recruitment and participants

This study was a part of a randomized controlled study investigating the efficacy of a new parenting focused prenatal intervention for pregnant women using substances. Women with singleton pregnancies < 22 gestational weeks (gwks) (between October 2011 and November 2014) referred to maternal outpatient clinic of Turku University Hospital, Finland due to 1) documented or self-reported illicit drug use, abuse of prescription medication or alcohol within three years prior to or during the present pregnancy, 2) and/or a sum score of  $\geq 3$  points on TWEAK alcohol screening [15] were interviewed by a psychiatric nurse. If the interview revealed a current problem and need for specialized care in pregnancy due to her substance use the woman was offered an opportunity to participate. Of the eligible women ( $n = 126$ ), 95 (75%) participated and gave written informed consent. All the subjects received standard care at a tertiary obstetric center. Collaboration with a social worker and psychiatric nurses started ad referral. The study was built into the clinical practice and was accepted by the Joint Ethical Committee of South-Western Hospital District and University of Turku.

### 2.2. Data collection protocol

A psychiatric nurse surveyed the women's substance use history with a modified European Addiction Severity Index (EuropASI) at referral and at each visit at the maternity clinic they were asked about their current substance use [16]. The participants filled in a questionnaire regarding their sociodemographic background and current life situation. Medical history, obstetric data and results of maternal urine drug tests were collected from the hospital records. The random urine drug screen included testing for the metabolites of amphetamine, cannabis, cocaine, opiates, methadone, benzodiazepines, buprenorphine. Creatinine levels were routinely measured to ensure sufficient concentration of the urine. Positive screening results were further analyzed with liquid chromatography-mass-spectrometry (LC-MS/MS) to eliminate false positive screening results. The results were interpreted while taking account of the prescribed medication used.

Meconium and urine samples were collected from the infants after birth and analyzed quantitatively with liquid chromatography-mass-spectrometry (LC-MS/MS). The most commonly used substances were assessed (morphine, 6-monoacetylmorphine, codeine, oxycodone, methadone, tramadol, buprenorphine, norbuprenorphine, amphetamine, methamphetamine, MDMA, MDA and tetrahydrocannabinol). The results of the meconium testing were interpreted considering the prescribed medication used during pregnancy and delivery. The newborns stayed at the hospital neonatal ward for a minimum of two days. They were closely observed regarding signs of neonatal abstinence syndrome. In case of any abstinence signs, the Finnegan scoring was used [17]. The infants scoring over eight points three times consecutively during 2 h were referred to the neonatal intensive care unit

(NICU) for treatment of withdrawal syndromes with morphine. Neonatal data was collected from electronic patient files (see Table 4).

### 2.3. Measures

The infants' neurobehavior was assessed with the Dubowitz scale 1–4 days after delivery by a trained physiotherapist [12]. The scale has 34 items subdivided into six categories (tone, tone patterns, reflexes, movements, abnormal signs, and behavior). A quantitative scoring system of the Dubowitz has been established earlier by Dubowitz et al. [18] Each of the 34 individual items was given an optimality score: an item falling below the cut-offs of the lowest 10th centile was identified as 'deviant' and below the 5th centile as 'abnormal'. An item falling above the 10th percentile was given a score of 1, an item falling between the 5th and 10th a score of 0.5 and below 5th a score of 0. For the six categories a compound score was calculated by summing up these individual item optimality scores. The total optimality score is the sum of the total scores of the six categories with the maximum value of 34, which is the total number of the individual items. Higher scores indicate better outcomes. The conversion takes the gestational age into account. The normative values derived from the study by Dubowitz were used as comparison values in the present study. The population-based sample of that study consisted of 224 low-risk, term newborn infants [18]. To enable comparison with the established normative values, preterm infants (< 37 gestational weeks) were excluded from the present study.

The infants with abnormal neuromotor behavior were followed-up by the physiotherapist every one to three months until the infant's motor development had normalized. The mothers were given instructions, how to support their infant's motor development.

Information regarding fetal exposure to substances was based on the pregnant woman's self-reporting and documentation in electronic patient files. If the participant reported substance use, gave positive urine screens, had needle marks indicating intravenous substance use or documented intoxications, the fetus was classified as exposed to substances. The fetus was considered as potentially exposed if there was clinical suspicion of maternal substance use, such as missed appointments or drug screens, but the use of substances could not be objectively verified. In case of no clinical evidence or suspicion of prenatal substance use, the fetus was categorized as unexposed.

### 2.4. Statistics

The statistical analyses were performed with the SAS/STAT® 9.2 software. The comparisons between the included mother-infant pairs ( $N = 54$ ) and the excluded mother-infant pairs ( $N = 22$ ) in the nominal variables were performed with a chi-square test or a Fisher's exact test, when appropriate. The comparisons between two groups in the non-normally distributed continuous variables were performed using a Mann Whitney  $U$  test. The normality of the distributions was tested with Shapiro-Wilk's test. Student's  $t$ -test with pooled variables was used to compare the study infants with normative data. The differences of Dubowitz optimality scores of infants between the exposed, potentially exposed and unexposed groups were tested with ANOVA. The maximum likelihood Fisher's scoring was used in logistic regression analysis to compare the infants needing physiotherapy and those not needing it.

## 3. Results

### 3.1. Attrition and exclusion

Ninety-five pregnant women were recruited, and 76 infants were delivered and included in the study. The neurobehavior of 54 infants was assessed with the Dubowitz and followed-up until one year of age. See Table 1 for attrition and Table 2 for comparison of the included and excluded patients. No children had low Apgar scores (< 5 at 1 min, < 7

**Table 1**  
Study participants and attrition.

Recruitment <i>n</i> = 95
Dropout because of pregnancy related reasons <i>n</i> = 5
Own decision <i>n</i> = 11
Logistical reasons <i>n</i> = 3
Deliveries <i>n</i> = 76
Excluded because of prematurity <i>n</i> = 8
Death <i>n</i> = 1
Logistical or technical reasons <i>n</i> = 13
Dubowitz examination and follow up <i>n</i> = 54

at 5 min), low cord pH (< 7) or signs of birth asphyxia or encephalopathy.

**3.2. Background and characteristics of the subjects**

The sociodemographic background and substance use history of the mothers of the 54 infants is presented in Tables 2 and 3. Ninety-four percent (*n* = 51) of the women were smokers at the time of getting pregnant, but 31 (61%) of them reported to have reduced smoking and 16 (31%) ceased completely during the pregnancy. In early gestation before being aware of their pregnancy, 59% (*n* = 32) reported substance use or substance use could be verified from other sources (urine drug screen, medical history record notes). After recruitment substance use was verified in 26% (*n* = 14) and potential fetal exposure based on clinical suspicion in 24% (*n* = 13). Of the 14 women with verified substance use, two had used only alcohol, three alcohol and drug(s), six a single drug and three more than one drug. The used drugs included opioids (*n* = 5), benzodiazepines (*n* = 3), cannabis (*n* = 3), stimulants (*n* = 2), LSD (*n* = 1) and tizanidine (*n* = 1). Substance use of two mothers could not be identified because of insufficient medical records. Eight mothers were on opioid substitution therapy with buprenorphine. The mean dose of buprenorphine decreased from 11 mg (range 4–14 mg) to 8 mg (0–12 mg) during pregnancy.

Meconium was successfully collected from 96% (*n* = 52) of the newborns. Only three meconium samples tested positive for drugs (one for amphetamine, two for opiates).

The somatic data of the neonates is presented in Table 4. All infants were monitored for withdrawal symptoms. Seven infants (13%) were transferred to the NICU because of withdrawal symptoms, five of them

**Table 2**  
Characteristics and comparisons between the included (*N* = 54) and the excluded (*N* = 22) mother-infant pairs.

Maternal socio-demographic background	Included mother-infant pairs ( <i>N</i> = 54)		Excluded mother-infant pairs ( <i>N</i> = 22)		Mann-Whitney U	<i>p</i>
	Mean (SD)	Median(range)	Mean (SD)	Median(range)		
Age (years)	23.2 (4.9)	22.5 (17–34)	27.2(6.0)	27.0 (18–40)	372.5	0.01*
Duration of substance use (years)	5.2 (3.6)	4 0.0 (0.5–17)	7.0 (6.9)	4 (0–28)	468.5	0.47
	<i>n/N</i> (%)		<i>n/N</i> (%)		<i>df</i>	<i>p</i>
Elementary education or less	28/50 (56.0%)		11/22 (50.0%)		1	0.22
Psychiatric comorbidity	41/54 (75.9%)		18/22 (81.8%)		1	0.31
Buprenorphine substitution for opioid addiction	8/52 (15.4%)		5/22 (22.7%)			0.51 <sup>a</sup>
Initial reason for referral from primary care						
Alcohol abuse	11/54 (20.4%)		3/22 (13.6%)			0.75 <sup>a</sup>
Alcohol and drug abuse	8/54 (14.8%)		1/22 (4.5%)			0.27 <sup>a</sup>
Drug abuse (single abused drug)	6/54 (11.1%)		1/22 (4.5%)			0.67 <sup>a</sup>
Poly drug use (more than one drug)	11/54 (20.4%)		5/22 (22.7%)			1.00 <sup>a</sup>
Poly drug and alcohol abuse	17/54 (31.5%)		12/22 (54.5%)	1	3.52	0.06
History of intravenous substance abuse	24/52 (46.2%)		10/22 (45.5%)	1	0.003	0.96
Hepatitis C	11/51 (21.6%)		7/22 (31.8%)	1	0.87	0.35
Smoking during pregnancy	51/54 (94.4%)		18/22 (81.8%)	1	2.98	0.08
Pregnancy data						
Nulliparous (first delivery)	40/54 (74.1%)		15/22 (68.2%)	1	0.27	0.60
Planned pregnancy	13/53 (24.5%)		9/21 (42.9%)	1	2.42	0.12
Verified fetal substance exposure in pregnancy	14/54 (25.9%)		11/22 (50%)	1	4.10	0.04*

\* *p* < 0.05.

<sup>a</sup> Fisher's exact test.

presented with clear neonatal abstinence syndrome, three of which needed morphine treatment.

**3.3. The Dubowitz neurological examination**

Only four infants (7%) reached optimal total optimality scores (total optimality scores 30.5–34.0) in Dubowitz in contrast with 95% in normative population. The mean total optimality score was lower (26.6) in these risk infants compared to the normative reference range (32.9), *p* < 0.001.

The subscale optimality scores were abnormally distributed in all six categories (see Tables 5a and 5b). In the comparison sample by definition only 10% of infants fell behind the subscale optimal scores. In the current study, depending on the subscale, 17 to 100% of the infants did not reach the optimal score. The “movement” subscale was found most distorted as none of the infants reached optimal scorings. Also, in the “reflexes” subscale only one fifth of the infants reached optimal values. The “abnormal signs” subscale presented closest to the reference values with 83% of the infants reaching optimal scoring.

The infants with documented intrauterine exposure to substances (*n* = 14), the infants potentially exposed (*n* = 13) and the unexposed infant (*n* = 27) scored similarly in the Dubowitz (*p* = 0.11).

**3.4. Evaluation of the need for physiotherapeutic follow-up**

Sixty-three percent (*n* = 34) of the newborns were clinically considered to need physiotherapeutic re-assessment or follow-up for reasons such as abnormal movements, trembling and hypotonia. At the age of three months, 41% (*n* = 14) of the infants initially needing physiotherapeutic re-assessment showed normal neuromotor development. At six months of age 76% (*n* = 26) of the infants and at 12 months 88% (*n* = 30) showed normal neuromotor function. During the 12-month follow-up none of the infants presented with signs of serious problems in motor development, such as cerebral palsy.

**4. Discussion**

In this study infants of mothers who were referred to hospital maternity clinic primarily due to a recent history or current substance use, were examined regarding their early neurobehavior. A majority of these infants (93%) were found to have suboptimal neurological findings in

**Table 3**  
Characteristics of the mothers of the 54 infants examined with the Dubowitz examination.

Gestational age at recruitment (weeks)	N (%)	Mean	SD	Range
	54	13	3.5	7–22
Initial reasons for referral from primary care				
Alcohol abuse	11 (20)			
Alcohol and drug abuse	8 (15)			
Drug abuse (single abused drug)	6 (11)			
Poly drug use (> 1 abused substance)	11 (20)			
Poly drug use and alcohol abuse	18 (33)			
<hr/>				
	N (total number of responses)		n	%
<hr/>				
Psychiatric comorbidity	54		41	76
Depression			21	40
Anxiety disorder			19	35
Personality disorder			9	17
Bipolar disorder			3	6
Psychotic disorder			3	6
Eating disorder			3	6
History of suicidality	53		34	63
Abused substances (self-reported, at the time of referral)	54			
Alcohol			31	57
Marijuana			14	26
Opiates			12	22
Stimulants (amphetamine/ecstasy)			11	20
Benzodiazepines			8	15
Designer drugs			3	6
Treatment for addiction disorder at the time of pregnancy	53			
Institutional treatment			10	19
Specialized addiction outpatient treatment			34	64
Psychiatric outpatient treatment			12	23
Opioid substitution treatment	54		8	15
Psychopharmacological treatment	54		21	39
Antidepressants (SSRI)			9	14
Antipsychotics			6	11
Benzodiazepines			10	19
Opioids (other than buprenorphine)			2	4
Other			4	7

six Dubowitz subscales. The “movements” and “reflexes” categories were most affected. Nearly all deviances in the early neuromotor performance normalized with age and no developmental disorders were diagnosed in the follow-up period of 12 months.

The study population was heterogenic. The study cohort consisted of mothers with opioid addiction, prescription drug misuse, alcoholism and use of other substances, which makes it hard to draw conclusions on the effects of single substance exposures. In addition, majority of them were smoking tobacco in early pregnancy. Prenatal tobacco exposure has been shown to affect the neonate's neurobehavior dose-responsively by worsening overall motor performance and increasing excitability, hypertonicity and stress/abstinence signs [19,20].

Interestingly, there were no differences in the Dubowitz scores between the subgroups of infants with confirmed intrauterine exposure, potential exposure and no exposure. This might be due to underreporting of substance use or small sub-group size, but also due to various confounding factors. Almost all women in this study suffered from psychiatric comorbidity. Many were on SSRI medication or antipsychotics, which may also affect the infant motor development [21]. Substance addiction combines with various medical and social adversities. Further, the large drop out ( $n = 27$ ) may cause bias. The often weak treatment and research commitment among substance abusing populations is familiar to clinicians working in the field.

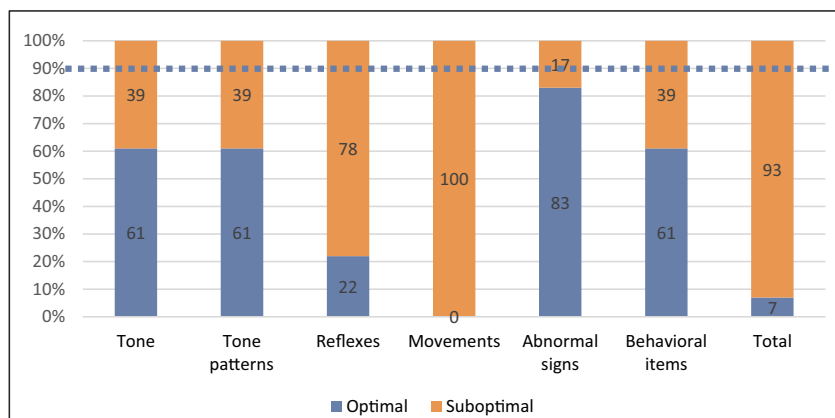
Polysubstance exposed infants have been shown to present with

**Table 4**  
Neonatal data.

	N	Mean	SD	Range
Gestational age (weeks)	54	39.7	1.1	38–42
Weight (grams)		3434	513	2430–4870
Weight Z score*		−0.5	1.1	−2.5–2.2
Head circumference (centimeters)	53	34.6	1.4	30.9–38.5
Head circumference Z score*		−0.4	1.0	−2.8–2.0
pH of umbilical artery	46	7.26	0.1	7.11–7.47
<hr/>				
	N	Median	SD	Range
Apgar score (1 min)	53	9	1.2	3–10
Apgar score (10 min)		9	0.5	8–10
Hospital stay after delivery (days)	53	4	9.1	2–58

\* According to national references derived from all singleton newborns in Finland.

**Table 5a**  
The percentages of infants in optimal/suboptimal ranges.



**Table 5b**  
Scores of the study infants in Dubowitz compared with the normative scores.

	Study group (n = 54)			Normative reference population (n = 224) <sup>13</sup>			p-value*
	Mean	SD	Min/max	Mean	SD	Min/max	
Total optimality score	26.6	2.5	21.0/32.0	32.9	1.8	25.0/34.0	< 0.001
Compound optimality scores by subscale	Mean	SD	Min/max	Normative			
Tone	8.6	1.5	3.5/10.0	> 9			
Tone patterns	4.5	0.7	2.0/5.0	> 5			
Reflexes	4.4	0.4	4.0/5.0	> 5			
Movements	0.4	0.6	0.0/2.0	> 3			
Abnormal signs	2.9	0.3	1.5/3.0	> 3			
Behavioral items	5.8	1.5	1.5/7.0	> 6			

\* t-test with pooled variables (Saphiro wilk's p = 0,881).

poorer motor performance [22]. In the present study, thirty-four out of 54 infants needed physiotherapeutic follow-up even though there was documentation of intrauterine substance exposure in only 26% of the infants. Most of the abnormalities of neurobehavior had resolved by the age of three months and in nine out of ten infants by the age of one year, which suggests a transient neurotoxic or withdrawal effect. This is in line with previous reports on cocaine exposed infants showing early deficits in motor development with a recovery to normal functioning by the age of 18 months [20]. A recent study using NNNS found altered neurobehavior in infants of buprenorphine-maintained mothers, which likewise improved over first month of life. [23]

The Dubowitz has been used in assessment of different risk infants but to our knowledge, there are no previous studies using it in assessment of infants of poly-substance using mother. [13,14] The Dubowitz is regarded as a reliable method for identifying children at risk for later neurodevelopmental problems and has been widely used in clinical settings for over two decades [12,24]. Over 7 items falling outside the Dubowitz's reference range when preterm infants were examined at term equivalent age predicted severe motor outcomes of diplegia or tetraplegia at the age of two years [25]. Even though many of the abnormalities observed in the neonate are known to improve with time, Setälä et al. found a correlation between the Dubowitz scores of preterm infants at term equivalent age and the Touwen examination at 11 years of age [26,27]. The Dubowitz has also been found to correlate well with infants' significant brain abnormalities in MRI [13]. Hence, abnormalities observed in the Dubowitz examination in the newborn are not diagnostic, but indicate a need for further evaluation [18,24]. Accordingly, it is feasible for screening at risk infants.

We used the earlier reported normative values acquired from 224 clinically healthy low-risk term infants as a reference, which may be considered a limitation. The infants in the present study were entirely Caucasian compared to 73% of Caucasian infants in the normative

reference group. The difference might have had some effect on the results.

The absence of blinding is also a limitation: the hospital staff including the physiotherapist knew they were handling infants of mothers with a history of substance use. This might have made them more vigilant noticing possible abnormalities. Also, a limitation common for all neurological examinations is that they reflect the neurobehavior of the infant at the time of the examination. The findings may fluctuate due to environmental factors such as feeding time [24].

The information on drug exposure was partly acquired by objective measurements available from hospital records and partly by self-reporting, which is known to be fairly unreliable [28,29]. We found the verification of the substance use challenging also because of the limitations of urine and meconium drug testing. Interestingly, the meconium tested positive for only three infants in this high-risk group. Meconium testing has a high sensitivity and specificity and it gives a broad time window of substance use as meconium excretion begins around the 12th gestation week [28]. Respectively, meconium cannot reveal the first trimester substance use, which might explain the incoherence with the information regarding early pregnancy substance use. Some false-negative meconium tests have previously been reported in analyses of opiates and cannabinoids, but the number of negative meconium samples in our study was too high to be accounted for with false-negatives [28]. There were two opioid negative samples from infants' whose mothers had been in opioid substitution therapy with buprenorphine during the first 20 weeks of their pregnancy. Ethanol metabolites do not show in meconium. It should be noted that despite a low number of positive meconium findings, the infants presented with abnormal neurobehavior. Thus, other risk factors besides intrauterine substance exposure probably contribute to the deviant findings.

## 5. Conclusion

In this study, infants born to mothers with substance abuse problem had strikingly abnormal performance in the Dubowitz neurological examination. This suggests that suboptimal findings in the Dubowitz should raise the clinicians concern for possible maternal substance use.

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## Declarations of interest

None.

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