Serum concentrations of psychotropic drugs in neonates as a PROgnOstic Factor for admission to the neonatology ward and withdrawal symptoms: PROOF-1

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The aim is to determine whether serum drug concentrations obtained from the neonate's umbilical cord can be used as a prognostic factor for admission to the neonatology ward and the occurrence of withdrawal symptoms. A retrospective observational monocenter cohort study was carried out among pregnant women using psychotropic drugs and their baby. Binary logistic regression was used for the multivariate analysis. Of the 186 neonates included, 22.6% ($n = 42$) were admitted to the neonatology ward, 6.5% ($n = 12$) because of withdrawal. Among women with therapeutic concentrations of psychotropic medication, 22.0% ($n = 5$) of the neonates had withdrawal symptoms. When comparing neonates with therapeutic versus undetectable drug concentrations, an odds ratio of 3.1 (95% confidence interval: 1.1–8.6) was found for admission to the neonatology ward and an odds ratio of 20.5 (95% confidence interval: 2.2–186.1) for the occurrence of withdrawal symptoms. Therapeutic concentrations of psychotropic drugs in neonates' umbilical cord blood correspond with higher odds for admission to the neonatology ward and the occurrence of withdrawal symptoms compared with neonates with undetectable drug concentrations. The measurement of drug concentrations in the neonate may contribute toward the general clinical assessment of the physician to predict the necessity of admission to the neonatology ward and the risk of withdrawal symptoms. *Int Clin Psychopharmacol* **00:000–000**

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Introduction

Approximately 3–11% of women have been estimated to have a major depression (Wemakor *et al.*, 2015). A prevalence of a major depressive episode of 7.1% was observed in women during the first 3 months postpartum (Gavin *et al.*, 2005). Untreated psychiatric disorders during pregnancy have negative effects on the unborn child and the mother. An association has been found between depression and low birth weight and premature birth related to higher cortisol concentrations in pregnant women with depression and stress (Oberlander *et al.*, 2006; Malm *et al.*, 2015; Wemakor *et al.*, 2015). Furthermore, higher rates of drug and alcohol abuse during pregnancy have been observed and contribute toward the negative effects on the unborn child (Wemakor *et al.*, 2015). After birth, an increased chance of poor bonding between mother and child has been observed in women with postpartum depression (Kieviet *et al.*, 2013). The risk–benefit ratio for continuing psychotropic drugs during pregnancy remains undetermined (Dutch Guideline, 2012). In-utero exposure of the neonate to psychotropic drugs increases the risk of certain congenital malformations, withdrawal symptoms, and toxic effects after birth (Malm *et al.*, 2015; Wemakor *et al.*, 2015). Conflicting evidence has been published on the association between in-utero antidepressant exposure and neurodevelopmental problems, such as autism (Cohen *et al.*, 2006; Gentile and Galbally, 2011). For each individual woman, a risk–benefit assessment should be performed to determine whether psychotropic drugs should be continued (Malm *et al.*, 2015; Wemakor *et al.*, 2015). Some studies found that discontinuation of antidepressants during pregnancy resulted in higher relapse rates. Cohen *et al.* (2006) found relapse rates of depressive symptoms of 68%. However, in a similar study by Yonkers *et al.* (2011), no difference in the development of a major depressive episode after discontinuation of antidepressants in pregnant women was observed compared with women who used antidepressants throughout pregnancy [hazard ratio = 1.14; 95% confidence interval (CI): 0.67–1.50]. Up to 50% of women restart their antipsychotics during pregnancy because of symptoms (Taylor *et al.*, 2016). Einarson *et al.* (2001) reported suicidal ideation in 33% of the women who discontinued

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their antidepressants. Similar percentages of 25% were observed by Taylor *et al.* (2016) in a population of women with psychotic and bipolar disorders.

In the Meander Medical Center, all pregnant women with psychiatric illnesses are treated by a multidisciplinary team to assess whether psychotropic drugs should be continued during pregnancy and breast feeding. The members of this team, a psychiatrist, a gynecologist, a pediatrician, a hospital pharmacist, a midwife, and a social worker, develop an individual treatment plan for the pregnancy, labor, and the period after childbirth.

As part of the treatment plan, all neonates of these mothers were born in the hospital and admitted for 3 days of observation at the maternity ward in the period 2006–2013. Occurrence of withdrawal symptoms or a general decline were reasons for transfer from the maternity ward to the neonatology ward for closer observation and, if necessary, treatment. Withdrawal symptoms may include feeding problems, irritability, hypotonia, hypothermia, respiratory distress, and tremors (Kieviet *et al.*, 2013; Oberlander *et al.*, 2014). Treatment of withdrawal generally consists of supportive care, and in rare and severe cases in phenobarbital administration, especially when convulsions are observed (Kieviet *et al.*, 2013). Predicting the risk of developing withdrawal symptoms could lead to earlier discharge of neonates with low risk and closer observation and earlier monitoring and treatment for neonates with high risk.

The aim of the study was to determine whether serum drug concentrations obtained from neonate's umbilical cord can be used as a prognostic factor for admission to the neonatology ward and occurrence of withdrawal.

Methods

Study design and data source

A retrospective observational monocenter cohort study was carried out. From 2006 to 2013, data were collected using the electronic patient files and laboratory system. As standard of care, the multidisciplinary team determined whether the psychotropic drug could be continued and whether dosage adjustments were necessary during pregnancy. Information of all women was collected and discussed by the multidisciplinary team. Pregnant women with a psychiatric disorder or at risk for a psychiatric disorder during pregnancy were introduced to the multidisciplinary team by their midwifes or gynecologist affiliated with the hospital. All the women using psychotropic drugs such as selective serotonin reuptake inhibitors (SSRI's; e.g. citalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), serotonin and noradrenaline reuptake inhibitors (e.g. venlafaxine), antipsychotics (e.g. haloperidol), and antimanic (e.g. lithium) were included in the analyses. All neonates of these women were admitted for 3 days at the maternity ward for observation. If the neonates had complications at birth, developed withdrawal symptoms, or had any other reason for admission to the neonatology ward, they were directly admitted or transferred to the neonatology ward. If five or less women were using the psychotropic drug, they were excluded from the analysis. This is the reason why no data are included on tricyclic antidepressants.

Parameters

The database used for the analyses included the following parameters: concentrations of psychotropic drugs in the neonates (umbilical cord), comedication use of the mother, Apgar scores after 1, 5, and 10 min, gestational age at birth, birth weight, venous umbilical blood pH, occurrence of withdrawal symptoms, and complications during labor and delivery. The serum drug concentrations of both the neonate and the mother were used to support therapy of the mother and well-being of the child. An analysis of the samples was carried out on routine analysis days, that is, once or twice a week.

For the analyses, maternal serum drug concentration and umbilical cord drug concentrations were subdivided into three groups: undetectable, subtherapeutic, and therapeutic serum drug concentrations. Reference concentrations were according to Dutch Guidelines (Commission Analysis and Toxicology of the NVZA, 2016). Serum drug concentrations of citalopram and venlafaxine presented in this article consist of concentrations of the drug and the most common metabolite. One cord serum drug concentration of venlafaxine was supra therapeutic. This was labeled as therapeutic for the analyses.

Endpoints

The primary endpoint of the study was admission to the neonatology ward due to of any cause. The secondary endpoint was the occurrence of withdrawal symptoms. Occurrence of withdrawal symptoms was determined by the pediatrician on the basis of clinical presentation. Other prognostic factors for admission to the neonatology ward were also evaluated and included.

Statistical analyses

For the univariate analyses, continuous variables were evaluated using analysis of variance. Bonferroni's post-hoc analysis was carried out to determine the relation in the specific groups. For categorical parameters, the χ^2 or Fisher's exact tests were used. To evaluate the combination of predictors of admission, multivariate binary logistic regression was performed. SPSS, version 22 (IBM Corp., Armonk, New York, USA) was used for the statistical analyses.

Results

General results

In total, 189 neonates from 187 pregnancies (two twins) in 176 mothers were included in the analyses. Most

Table 1 Characteristics of the mothers ($N = 187$[a,b])

Medication (n)	Gravidity [mean (SD)]	Age [mean (SD)] (years)	Comedication use [n (%)]
SSRI (160)	2.3 (1.4)	31.5 (5.2)	6 (3.8)
Antipsychotic (6)	3.7 (1.0)	37.0 (4.1)	1 (16.7)
Antimanic (8)	2.25 (1.0)	29.9 (5.0)	0
SNRI (15)	2.4 (0.9)	32.2 (5.2)	0

SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Every pregnancy is included separately as medication was not constant.
[b]Two twins were born.

mothers used an SSRI (84.6%) or an serotonin and noradrenaline reuptake inhibitor (7.9%). Antipsychotic and antimanic medication accounted for 4.8 and 4.2%, respectively. Seven (3.7%) mothers used more than one psychotropic drug. The characteristics of the mothers are shown in Table 1. No significant differences were found in gravidity, age, or comedication use between the medication groups. Three neonates of the 189 were excluded from any further analyses because of the absence of the umbilical cord drug concentrations.

Admission to neonatology ward

Of the 186 neonates, 22.6% ($n = 42$) were admitted to the neonatology ward. In 14.0% ($n = 26$), therapeutic drug concentrations were measured. Of the neonates with therapeutic drug concentrations, 42.3% ($n = 11$) were admitted to the neonatology ward. In the subtherapeutic drug concentration group, 19.2% ($n = 14$) of the neonates were admitted to the neonatology ward. Admission to the neonatology ward did not differ between the medication groups, with the exception that in the antimanic group, no neonate was admitted (Table 2).

In the multivariate analysis (Table 3), therapeutic drug concentrations in the umbilical cord were a prognostic factor for admission to the neonatology ward [odds ratio (OR) = 3.1; 95% CI: 1.1–8.6] compared with undetectable serum concentrations. The other prognostic factor for admission to the neonatology ward was gestational age equal to or less than 35 weeks. Apgar scores below 7 after 5 min were of borderline statistical significance. Venous pH of umbilical cord as a measure of asphyxia was excluded from the analyses because of the low number ($n = 1$) of neonates with venous pH below 7.05. This neonate was admitted to the neonatology ward.

Other reasons for admission to the neonatology ward besides withdrawal symptoms were hypoglycemia ($n = 12$), decrease in saturation and/or need for ventilation ($n = 11$), meconium in amniotic fluid ($n = 6$), and groaning ($n = 6$). Other less common reasons were nasal stuffiness ($n = 3$), dyspnea ($n = 2$), bradycardia ($n = 2$), infection ($n = 1$), and nuchal cord ($n = 1$). Five neonates had multiple reasons for admission.

Occurrence of withdrawal symptoms

In total, 12 (6.5%) neonates were admitted because of withdrawal symptoms. Of all neonates with therapeutic drug concentrations, 19% ($n = 5$) had withdrawal symptoms. For the neonates with subtherapeutic concentrations, 8.2% ($n = 6$) developed withdrawal symptoms and 1.1% ($n = 1$) of the neonates had undetectable concentrations. Thus, the percentage admission because of withdrawal symptoms was higher in the therapeutic drug concentrations group compared with the subtherapeutic and undetectable groups ($P < 0.05$).

In the multivariate analysis, neonates with therapeutic serum concentrations had 20.5 (95% CI: 2.2–186.1) higher odds for the occurrence of withdrawal symptoms compared with neonates with undetectable serum concentrations (Table 3). No other parameters were prognostic factors for the occurrence of withdrawal symptoms.

Other outcomes

The average birth weight in the therapeutic group was 3058 g. In the subtherapeutic group and the undetectable drug concentration group, the average birth weight was

Table 2 Characteristics and outcomes of infants exposed to psychotropic medication *in utero*

Medication groups ($n = 186$)	Birth weight [mean (SD)] (g)	Sex: female [n (%)]	Gestational age [mean (SD)]	spontaneous labor [n (%)][a]	Apgar score < 7 at 5 min [n (%)]	Admission to neonatology ward [n (%)]	Admission to neonatology ward [mean (SD)] (days)	Withdrawal symptoms [n (%)]
SSRI (157)	3297 (556)	51.6 (81)	271.7 (11.5)	76.0 (114)	5.1 (8)	24.2 (38)	7.6 (6.8)	5.8 (9)
Antipsychotic (9)	3457.2 (469)	66.7 (6)	280.7 (7.9)	88.9 (8)	0 (0)	22.2 (2)	3.5 (0.7)	11.1 (1)
Antimanic (8)	3404 (314)	50.0 (4)	274.5 (12.3)	50.0 (4)	0 (0)	0 (0)	0 (0)	0 (0)
SNRI (15)	3392 (507)	40.0 (6)	268.3 (7.8)	93.3 (14)	0 (0)	20.0 (3)	4.7 (5.5)	13.3 (2)
Serum concentrations								
Undetectable (87)	3333 (557)*	51.7 (45)	272.5 (12.3)	79.5 (66)	2.3 (2)	19.5 (17)[$]	9.4 (8.2)	1.1 (1)[^]
Subtherapeutic (73)	3386 (521)*	53.4 (39)	272.4 (10.4)	73.2 (52)	4.1 (3)	19.2 (14)[$]	5.7 (6.3)	8.2 (6)[^]
Therapeutic (26)	3058 (478)*	50.0 (13)	268.1 (10.1)	80.0 (20)	7.7 (2)	42.3 (11)[$]	5.6 (3.1)	19.2 (5)[^]

SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
Post-hoc analysis Bonferroni, therapeutic vs. subtherapeutic, $P = 0.026$ and therapeutic vs. undetectable, $P = 0.068$.
[a]Nonspontaneous births were defined as vacuum extraction, planned, and unplanned cesarean section.
*Significant difference between groups, $P = 0.028$ (analysis of variance).
[$]Significant difference in admission to the neonatology ward, $P = 0.035$ (χ^2-test).
[^]Significantly difference in withdrawal symptoms, $P < 0.05$ (Fisher's exact test).

Table 3 Results of univariate and multivariate analyses for admission to the neonatology ward and withdrawal symptoms

	Admission to the neonatology ward	Withdrawal symptoms[b]
	Multivariate [OR (95% CI)]	Univariate [OR (95% CI)]
Gestational age (weeks)		
≤35	19.3 (3.6–101.6)[#]	4.8 (0.9–27.1)
36–37	1.9 (0.8–4.9)	0.99 (0.2–4.9)
≥38	Reference	Reference
Apgar score after 5 min[a]	5.1 (1.0–26.0)	2.1 (0.2–19.0)
Serum drug concentrations umbilical cord		
Undetectable	Reference	Reference
Subtherapeutic	0.9 (0.4–2.2)	7.7 (0.9–65.5)
Therapeutic	3.1 (1.1–8.6)[#]	20.5 (2.2–186.1)[#]
Birth weight	–	1 (0.9–1)
Sex	–	1.1 (0.3–3.4)
Medication		
SSRI	–	Reference
Antipsychotic	–	–
Antimanic	–	2.0 (0.23–18.1)
SNRI	–	2.5 (0.5–12.9)
Labor	–	0.3 (0.04–2.3)

CI, confidence interval; OR, odds ratio; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
[a]Apgar score < 7 vs. ≥ 7.
[b]In the multivariate analysis, the only variable was serum drug concentration; therefore, the results are not shown in the table.
[#]$P < 0.05$, significant.

3386 and 3333 g, respectively (Table 2). A significant difference was found between the drug concentration groups for birth weight ($P < 0.05$). In the group with therapeutic drug concentrations, 7.7% ($n = 2$) had an Apgar score below 7 compared with 2.3% ($n = 2$) in the group with undetectable drug concentrations (Table 2).

In 5.1% of the neonates of mothers using SSRIs, Apgar scores below 7 were found after 5 min. In the other groups, no Apgar scores below 7 were observed after 5 min.

Discussion

To our knowledge, this is the first study relating neonates' drug concentrations from umbilical cords to admission to the neonatology ward. Results showed higher odds for admission to the neonatology ward and the occurrence of withdrawal symptoms among infants with therapeutic serum concentrations from umbilical cord compared with infants with undetectable serum drug concentrations.

In the literature, several studies showed 20–50% admission rates because of withdrawal symptoms of neonates exposed *in utero* to psychotropic drugs (Hendrick *et al.*, 2003; Levinson-Castiel *et al.*, 2006; Oberlander *et al.*, 2006; Ter Horst *et al.*, 2006). In our study, a general admission rate of 22.5% was found and only 6.5% of the neonates were admitted with withdrawal symptoms. Overall, 20% of neonates with therapeutic serum drug concentrations had withdrawal symptoms, corresponding with other studies. As the standard of care, serum drug concentrations of the women during pregnancy were obtained. When high drug concentrations were measured, dose adjustment was considered. This could result in lower effective serum drug concentrations and milder or fewer withdrawal symptoms in the neonate compared with the other studies. Unfortunately, in previous studies, no drug concentrations in cord blood were obtained. The difference in prevalence between our study and those in the literature may also be because of the determination of withdrawal symptoms. In the period 2006–2013, the Finnegan score (Levinson-Castiel *et al.*, 2006) was not used routinely in this population neonates as the standard care in the Meander Medical Centre. Withdrawal symptoms were determined on the basis of clinical presentation and the professional judgment of the pediatrician. This could result in an under-reporting compared with studies that used the Finnegan score systematically.

Although the drug concentrations of the neonates were intended for clinical care, it proved practically impossible to use these results for decision-making because the analysis was not frequent enough. Thus, the decision to admit an infant to the neonatology ward was not always made on the basis of these concentrations.

In our study, a high percentage of neonates with therapeutic drug concentrations had withdrawal symptoms. Kieviet *et al.* (2013) found withdrawal symptoms with subtherapeutic serum concentrations and toxicity in neonates with therapeutic drug concentrations. Possibly, neonates with high and therapeutic drug concentrations developed toxicity instead of withdrawal symptoms in our study. Differentiation between withdrawal symptoms and toxicity is challenging (Kieviet *et al.*, 2013). Symptoms such as irritability, tremors, jitteriness, myoclonia, and respiratory distress occur with toxicity as well as with withdrawal symptoms. With toxicity, hyperthermia, sweating, hyperreflexia, and diarrhea are also observed. Furthermore, signs of toxicity are specific for the psychotropic drug used, resulting in a wide range of potential symptoms in our study population. Feeding difficulties, vomiting, and sleeping difficulties are more frequently observed during withdrawal. Time of onset of symptoms is one of the most objective characteristics to distinguish both. Toxicity is observed immediately after birth and withdrawal symptoms start 8–48 h after birth depending on the half-life of the psychotropic drug (Kieviet *et al.*, 2013). Unfortunately, the time of onset of symptoms was not recorded in the medical file.

As expected, the other prognostic factor for admission to the neonatology ward was gestational age at birth. All neonates with gestational age below or equal to 35 weeks were routinely admitted to the neonatology ward, explaining it as a prognostic factor. In the univariate analysis, Apgar score after 5 min was also a prognostic factor. In the multivariate analysis, Apgar scores after

5 min below 7 were of a similar magnitude, but of borderline significance. This might be explained by the low number ($n = 7$) of neonates with Apgar scores below 7. The low numbers of neonates admitted to the neonatology ward could explain the wide CIs of the ORs in our study.

Venous blood pH from umbilical cord was excluded from the analyses as described previously. As a sign of asphyxia, the venous blood pH (arterial blood pH was available only for a few neonates) might be another prognostic factor for admission to neonatology ward (Dutch Guideline, 2012).

Our study shows the prognostic value of drug concentrations of neonate for admission to the neonatology ward and withdrawal symptoms. Other prognostic values that we found were gestational age and Apgar scores below 7 after 5 min (borderline significance). In our study, no information was obtained on the severity of the psychiatric illnesses of the mothers during pregnancy. Maternal depression could be a prognostic factor for admission to the neonatology ward. In a retrospective population-based data analysis of 4296 women, the results showed that depression before pregnancy and maternal depression were predictors for neonate ICU admission, with adjusted OR of 1.66 (95% CI: 1.12–2.45) and adjusted OR of 2.48 (95% CI: 1.71–3.60), respectively (Latendresse *et al.*, 2015).

Conclusion

Neonates with therapeutic umbilical cord serum drug concentrations of psychotropic drugs had higher odds for admission to the neonatology ward and for withdrawal symptoms compared with neonates with undetectable serum concentrations. Umbilical cord serum drug concentrations of the neonate may contribute toward the general clinical assessment of the physician to predict the occurrence of withdrawal symptoms and the necessity of admission to the neonatology ward instead of the maternity ward. Further prospective research is needed to confirm our results in a large population. To prepare pregnant women in an earlier stage of their pregnancy, we would like to investigate whether maternal serum concentrations obtained during pregnancy are a prognostic factor for occurrence of withdrawal and admission to the neonatology ward as well.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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