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Neonatal adaptation following intrauterine antidepressant exposure: assessment, drug assay levels, and infant development outcomes

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BACKGROUND: Although a meta-analysis has confirmed the association between antidepressant exposure *in utero* and subsequent poor neonatal adaptation, few identified studies included drug levels or standardized measures and only two studies followed up children who developed symptoms beyond infancy.

METHODS: The study draws on the Mercy Pregnancy and Emotional Wellbeing Study and reports on 42 women/infant pairs at delivery. In all, 31 women continued to take antidepressants until delivery and 11 ceased earlier in pregnancy. Poor neonatal adaptation was assessed twice daily for up to 6 days by using the Neonatal Abstinence Scoring System (NASS). Drug levels were analyzed in umbilical cord blood and maternal blood obtained at delivery.

RESULTS: In total, 76% (32 of 42) of neonates exposed to antidepressants had symptoms observed on the NASS. These symptoms occurred up to 5 days postpartum with 25% having symptoms that persisted for more than 3 days. The most frequent symptoms were correlated most closely to antidepressant drug levels. Elevated NASS scores were found to be associated with poorer fine motor development at 6 months of age.

CONCLUSIONS: Poor neonatal adaptation may be more common than previously recognized. The NASS was observed to be an effective assessment and monitoring measure. Research following symptomatic infants beyond the neonatal period is required.

Since first reported by Chambers *et al.* in 1996, there have been consistent findings of poor neonatal adaptation following antidepressant exposure *in utero* (1). Subsequent studies have found an increased risk of such symptoms with higher medication doses (2) and with specific antidepressants (3). Poor neonatal adaptation syndrome (PNAS) is known to present in distinct symptom clusters including gastrointestinal, neurological, and respiratory symptoms (2). A meta-analysis in 2013, limited to case–control and cohort studies, identified 12 studies and found consistent evidence of PNAS, respiratory distress, and tremors associated with antidepressant exposure in pregnancy (4).

There are three consistent questions that remain unanswered when examining the relationship between poor neonatal adaptation and antidepressant exposure *in utero*. The first is how to best assess neonates for poor neonatal adaptation following antidepressant exposure. Although only three studies in the recent meta-analysis utilized a standardized scoring system (5), the Neonatal Abstinence Scoring System (NASS) was used in two of the three, and this measure is also frequently recommended in hospital guidelines (4). The NASS was originally developed for the assessment of neonatal opiate withdrawal, and one recent study has attempted to validate an adapted version in infants exposed to antidepressants *in utero* (6). It is worth noting that in this study the cross-validation by a pediatrician was not blinded, and the identification of items and validation of the modified version was within the same sample, suggesting that further validation of this adapted NASS is required (6). A study that administered the NASS in a healthy population of neonates found that high-pitched cry, short sleep, vomiting, and sneezing were the most common observed symptoms (7). However, this study does not report scores or frequencies across their sample. The authors conclude that their findings do support the use of the NASS to identify pathological symptoms in neonates.

The other standardized scale identified within the meta-analysis was the Serotonin Syndrome Scale used by Laine *et al.* (4,8). This scale was developed for measuring symptoms related to the serotonin syndrome in adults taking antidepressants and neither validated for pediatric population nor for antidepressant exposure *in utero* (8,9). Therefore, it is currently unclear how to best assess and monitor poor neonatal adaptation symptoms following antidepressant exposure.

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The second question is what process underlies these observed symptoms. Two explanations have been offered: serotonin toxicity or discontinuation at the time of birth or a distinct neurobehavioral effect from exposure of the fetal brain to antidepressants *in utero*. Within the most recent meta-analysis (4), three studies measured drug levels as well as symptoms (8,10,11). None of these studies found a clear relationship between maternal or neonatal drug levels and symptoms. However, a small study of venlafaxine, not included in the meta-analysis, examined levels in the neonate over days and found that as levels decreased symptoms in the neonate increased (12). A more recent study examined the levels of a serotonin metabolite, 5-HIAA, in neonatal urine and found higher levels in neonates with PNAS compared with those without PNAS (13). These few studies are not sufficient to draw firm conclusions as to whether poor neonatal adaptation symptoms represent drug withdrawal or toxicity at birth or are caused by an earlier impact on the neurodevelopment of the fetus.

The third question is whether these symptoms have any impact on the long-term health and well-being of the infant and the child. It has been well established that the acute symptoms have a short duration and are self-limiting, requiring only observation and supportive management (4,11). What is unclear is whether there are longer-term associations between the presentation, intensity, or duration of these symptoms and poorer infant growth (14) and development (15,16) that could be attributed specifically to PNAS, and which goes beyond the effect of the exposure to depression *per se*, or the use of an antidepressant in pregnancy.

The aim of this study was to examine the use of the NASS in neonates exposed to antidepressants *in utero* through repeat measurement by two different groups of health professionals and by examining the relationship between symptom patterns and clusters to maternal and neonatal drug levels. The NASS was selected as the assessment instrument in this study, as it is the most widely used and the only scale to have any validation for neonates' exposure to antidepressants. A second aim was to examine whether symptom severity or progression was accounted for by antidepressant levels at birth in maternal as well as in umbilical cord blood. Third, the study also aimed to add to the very limited information on long-term follow-up by including data on developmental outcomes from infants in the cohort at 6 months of age.

METHODS

Participants

This study draws on data from the Mercy Pregnancy and Emotional Wellbeing Study (MPEWS), which has been comprehensively described in a paper detailing the cohort profile, demographics, and study design (17). In brief, the MPEWS study uses a selected cohort design with two clinical groups and a comparison control group. The criteria for recruitment of the two clinical groups were as follows: women formally diagnosed with depression (past and current), using the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-Fourth-Text Revision according to Diagnostic and Statistical Manual of Mental Disorders-Fourth criteria, and women on antidepressant medication in pregnancy. In addition, a non-depressed pregnant group was also recruited from the general hospital population as a control group. This paper uses data from the antidepressant participants only, as depicted in **Figure 1**. These women were recruited before gestational week 20 and were taking an antidepressant at the time of recruitment. Recruitment commenced in September 2012 and was completed in October 2014 with the last participant delivering in late May 2015 (**Tables 1 and 2**).

The Mercy Health Human Research Ethics Committee approved the study, and a written informed consent statement was obtained from each woman. Inclusion criteria were being less than 20 weeks pregnant and English proficiency. Women who developed pregnancy complications were not excluded. Participants were excluded if they met Diagnostic and Statistical Manual of Mental Disorders-Fourth-Text Revision criteria for bipolar or psychotic disorders, substance abuse disorder, child protection involvement, intellectual disability, serious pre-existing physical illness, and psychiatric illness requiring current acute inpatient admission.

Antidepressant Use

Antidepressant type, usage, dosage, and timing were assessed by a self-report questionnaire at recruitment and again in the third

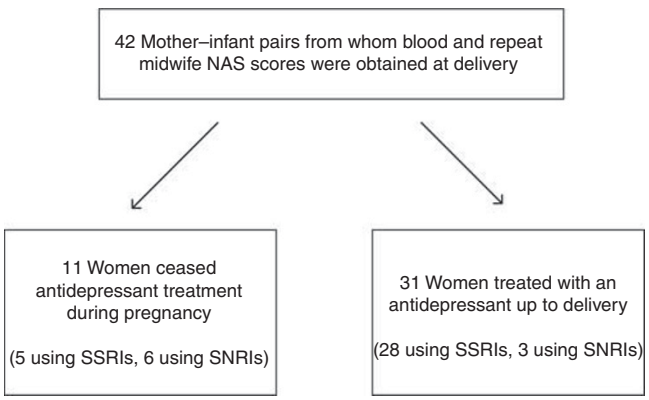

Figure 1. Flow chart showing the inclusion of women in the study. In the 31 women using antidepressants at delivery, the following drugs were used: citalopram, escitalopram, fluoxetine, paroxetine, sertraline, desvenlafaxine, venlafaxine, and duloxetine. Further details are in Galbally *et al.* (17).

Table 1. Demographics and birth outcomes for mothers using antidepressants ($N = 42$)

Demography	Mean (SD) or *N* (%)
Maternal age (years)	32.9 (4.4)
Alcohol use	12 (28.6%)
Smoking	7 (16.7%)
Sertraline equivalent dose, third trimester (mg/d)	79.9 (65.8)
Maternal antidepressant concentration ratio[a]	0.26 (0.28)
Fetal antidepressant concentration ratio[a]	0.18 (0.20)
Gestational age at delivery (weeks)	38.6 (1.6)
Infant birth weight (kg)	3.3 (0.5)
Infant birth length (cm)	49.9 (2.4)
Infant birth head circumference (cm)	34.1 (1.5)

[a]Ratio between the measured concentration and the concentration in the middle of the therapeutic range for the same drug.

Table 2. Number of infants experiencing NASS symptoms following birth ($N = 42$)

	Days following birth					
	1	2	3	4	5	6
CNS						
Crying	0	0	1	0	0	0
Sleeping after feeds	13	12	11	4	1	0
Moro reflex	0	1	1	0	0	0
Tremor	5	4	6	1	0	0
Muscle	1	1	1	0	0	0
Excoriation	0	0	0	0	0	0
Myoclonic	0	0	0	0	0	0
Convulsions	0	0	0	0	0	0
GIT						
Sucking	0	0	0	1	0	0
Feeding	3	5	3	1	0	0
Regurgitation	2	1	3	0	0	0
Stools	0	0	0	0	0	0
Other						
Sweating	0	1	0	0	0	0
Fever	2	1	1	1	0	0
Yawning	0	1	0	0	0	0
Mottling	0	0	0	0	0	0
Nasal	2	0	1	0	0	0
Sneezing	1	1	1	0	0	0
Nasal flaring	0	0	0	0	0	0
Respiratory	1	2	2	0	0	0
Total number of symptoms	30	30	31	8	1	0

CNS, central nervous system; GIT, gastrointestinal tract; NASS, Neonatal Abstinence Scoring System.

trimester of pregnancy. Self-report data were confirmed via hospital records checked at delivery. As the majority of participants were on sertraline, dosages were converted to sertraline equivalent doses according to the procedure outlined in Bezchlibnyk-Butler *et al.* (17,18).

Drug Assays

Maternal blood and cord blood were collected at delivery and stored for drug assay levels. The cord blood was collected by midwives at the delivery suites of the Mercy Hospital from the umbilical vein immediately following delivery and processed within 1 h of delivery. Blood collected was centrifuged and the plasma stored at −80 °C within 1 h of collection.

The selective serotonin reuptake inhibitors (SSRIs) citalopram, escitalopram, fluoxetine, norfluoxetine, paroxetine, and sertraline were analyzed with liquid chromatography–mass spectrometry within our laboratory. The serotonin and noradrenaline reuptake inhibitors (SNRIs) duloxetine, venlafaxine, and desvenlafaxine were analyzed with ultrahigh performance liquid chromatography–tandem mass spectrometry. The SSRI methods are described in detail previously (19), whereas the SNRI methods are based upon the same principles as described in another publication from our analytical laboratory (20).

All substances were extracted from serum with liquid–liquid extraction. Citalopram and escitalopram were extracted using hexane, butanol, and acetonitrile. Paroxetine was extracted using dichloromethane and isopropanol. Fluoxetine, norfluoxetine, and sertraline were extracted using butyl chloride. Duloxetine was extracted using acetonitrile and methanol. Venlafaxine and desvenlafaxine were extracted using acetonitrile, methanol, and formic acid. Deuterated internal standards were used. SSRIs, venlafaxine, and desvenlafaxine were separated on C18 columns, whereas duloxetine was separated on an Acquity UPLC HSS T3 column (Waters, Milford, MA). SSRIs were quantified on an Agilent MSD 1100 LC-MS system (Agilent Technologies, Palo Alto, CA), whereas SNRIs were quantified on a Xevo TQ-S Tandem-Quadrupole MS System (Waters).

The limits of quantitation were 5 nmol/l for sertraline, 10 nmol/l for citalopram, escitalopram, paroxetine, and duloxetine, 20 nmol/l for venlafaxine and desvenlafaxine, and 50 nmol/l for fluoxetine and norfluoxetine. The methods were linear in the concentration ranges achieved. Accuracy was controlled routinely with external control samples, and precision was calculated from the quality-control samples. The interassay coefficients of variation were less than 10%. To compare concentrations across the various antidepressants, a drug level measured in a sample was standardized by relating it to the middle of the therapeutic range of that drug (21). Thus, the degree of infant exposure could be estimated, irrespective of the specific antidepressant used by the mother.

Neonatal Adaptation

Poor neonatal adaptation was measured in antidepressant-exposed neonates through repeated administration of the NASS (5). This scale was developed by Finnegan for opiate withdrawal in neonates and consists of eight items for central nervous system (CNS) symptoms (e.g., high-pitched cry, tremor, and convulsions), four items for gastrointestinal symptoms (GIT; e.g., poor feeding and loose stools), and eight items for others (OTHER; e.g., fever, changes to respiratory rate, and sweating), with a total of 20 items (5,22). Each item has a maximum score ranging from 1 to 5. The neonates were assessed using the NASS by midwives twice daily for at least 3 days or until discharged. At 24 h post delivery, a pediatrician administered the NASS at the same time as the midwife. Both were blinded to each other's scores.

Developmental Assessment at 6 Months of Age

Infants were assessed at 6 months of age using the Ages and Stages Questionnaire, third edition (23), which was reported by the primary caregiver (typically the mother). This widely used screening tool uses 30 items and assessed the following areas of child development: including the subscale domains of Communication, Gross Motor, Fine Motor, Problem Solving, and Personal–Social.

Statistical Analysis

The data derived from the repeated measurement of the NASS were analyzed using latent growth curve modeling (LGM). Latent growth curve modeling conceptualizes change as a function of two latent factors: an intercept and a slope term. The intercept factor represents the severity of symptoms at the first time of measurement, whereas the slope factor represents the amount to which that severity increases or decreases at each successive measurement. The slope factor can be further constructed to represent a quadratic function for curvilinear changes in symptom severity. Alternatively, the model can be estimated without the slope factor, representing no change from baseline severity over time.

Analyses were conducted using Mplus version 7.4 with robust maximum-likelihood estimation in order to account for non-normal distributions. Missing data were accounted for using full-information maximum likelihood estimation. Changes in fit between models were assessed using scaled log-likelihood difference testing and the Bayesian Information Criterion. To account for individual variation in the specific timing of observation (infants observed at slightly

different intervals on the ward following birth), the linear and quadratic slope factors were parameterized using the hours since birth as random effects.

Each model of change (intercept-only, linear, and quadratic) was fitted to the NASS Total, CNS, GIT, and OTHER scores, with changes in fit statistics used to assess the most accurate model of change for each. Maternal and fetal antidepressant levels at the time of birth were entered as predictors of intercept, slope, and quadratic curve scores to assess their impacts on symptom severity and progression. Gestational age at birth, infant weight at birth, and alcohol and cigarette exposure during pregnancy (0 = no, 1 = yes) were entered as control variables.

Once the best-fitting model of change was determined, factor scores for the latent growth variables were estimated for each individual. These factor scores then represent each individual's "score" on the latent growth variables and can be used as outcomes when assessing the effects of covariates. By using this approach, the effects of antidepressant levels and other control variables on the progression of NASS symptoms can be assessed without also having to estimate the full growth model. Given the small sample size, reducing the number of parameters that need to be estimated in a given model improves the reliability of the results.

RESULTS

At recruitment there were 52 pregnant women treated with an antidepressant within a cohort of 282 women recruited. None of the women who took antidepressants in pregnancy also took antipsychotic medication in pregnancy, and only one woman took a benzodiazepine (diazepam). Only women who had taken antidepressants in pregnancy were administered the NASS. In total, 40 (78%) women used an SSRI, whereas 11 (22%) women used a SNRI. One participant changed from one SSRI to another during pregnancy. Of those babies exposed to antidepressants in pregnancy, only two babies met criteria for intrauterine growth restriction—one still exposed at delivery and one no longer exposed at delivery.

When comparing those women on an antidepressant at recruitment within the study to the rest of the cohort at baseline, there was no significant difference in age and household income in pregnancy (17) See **Table 1**.

One-way ANOVAs showed no significant differences between the three groups in Apgar scores at 1 min ($F(2,263) = 0.076$, $P = 0.927$), 5 min ($F(2,263) = 2.160$, $P = 0.117$), or 10 min ($F(2,5) = 0.781$, $P = 0.507$).

In 42 of the 51 women followed to delivery, maternal blood and cord blood were obtained and repeat NASS scorings were performed. Of these 42, 31 women had used antidepressants until delivery, whereas 11 had stopped using them earlier during pregnancy. Of these 11, 10 women had ceased antidepressants in pregnancy before third trimester. Of the 42 mothers, 36 breastfed within 5 days of birth and 27 reported still taking antidepressants while breastfeeding. Of the 42 women, their parity at recruitment, defined as the number of births after 20 weeks' gestation before this pregnancy, was 30 were nulliparous in this pregnancy, 9 were primiparous, and 3 were multiparous.

In total, 32 infants experienced withdrawal symptoms within 5 days of birth, 30/31 (97%) of the neonates exposed at birth and 2/11 (18%) of those not exposed at birth. Sleeping soon after feeding was the most common (experienced by 21), followed by tremors (experienced by 12) and feeding difficulties (experienced by 8). Of the 32 infants who experienced withdrawal symptoms, 17 experienced the same symptom for 2 or more consecutive days and eight infants for 3 or more days. Of those eight infants, six experienced sleeping soon after feeding and two experienced tremors See **Table 2**.

For the 11 infants who were not exposed at delivery, seven displayed a symptom on the NASS. Sleeping soon after feeding was experienced by all seven infants. One infant also experienced tremor and regurgitation, another also displayed fever, respiratory difficulties, crying, and sweating symptoms. Only one infant experienced the same symptom (sleeping) for 2 consecutive days.

No infant experienced excoriation, myoclonic jerks, convulsions, loose/watery stools, mottling, or nasal flaring within 6 days following birth.

In total, 20 infants were also assessed by a pediatrician, of whom 15 had the time of the assessment recorded. These 15 ratings were compared with the closest possible midwife's rating, with Cohen's Kappa used as a measure of inter-rater agreement. These statistics should, however, be interpreted with caution, given the very small sample size. Significant levels of agreement between the midwife and the pediatrician were seen for CNS ($\kappa = 0.413$, $P < 0.001$) and GIT ($\kappa = 0.398$, $P < 0.001$) items, but not for the OTHER items ($\kappa = -0.006$, $P = 0.896$). Disagreement was seen in the OTHER ratings of two infants, where the midwives noted respiratory difficulties and the pediatrician did not.

Unconditional Growth Models

The next stage of the analyses looked at the progression of the NASS symptoms after birth. As only one infant experienced symptoms at 5 days, and none at 6 days, 4 days was chosen as the time window. Fit statistics for all tested models are reported in **Supplementary Table S1 online**.

As shown in **Supplementary Table S1**, NASS total scores showed the best fit with an intercept-only model of change, indicating that infants presented with an average NASS total of 1.23, and that this did not significantly change in the following days. Plots of the observed and estimated progressions of NASS total scores are presented in **Figure 2**. Similar results were seen with CNS, GIT, and OTHER scores, all showing the best fit with intercept-only models of change. These plots of observed and estimated progressions of symptoms across the days following birth for CNS scores, GIT scores, OTHER scores, and Sleep subscale score are contained in **Supplementary Figures S2–S5**.

Conditional Growth Models

Factor scores for each of the intercept growth models were then estimated. Significant relationships were seen between NASS total score and both maternal (unstandardized $b = 0.139$, $P = 0.002$) and fetal ($b = -0.164$, $P = 0.002$) levels. No significant relationships were seen with gestational age at

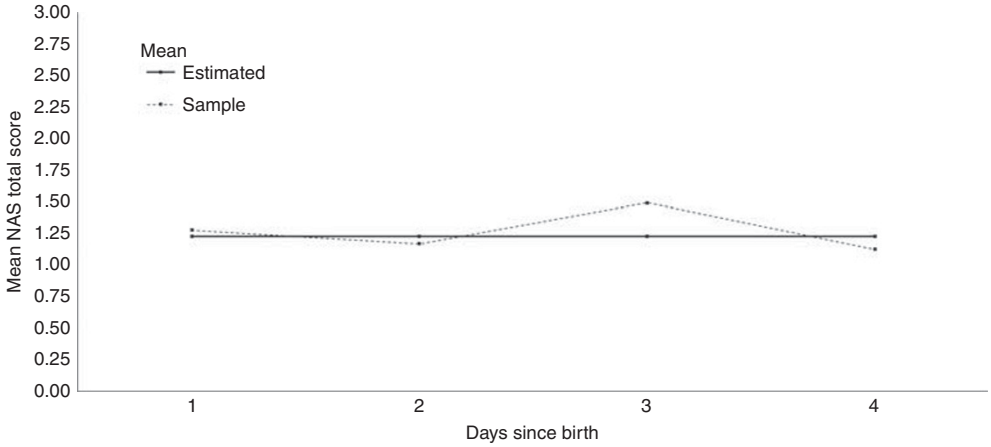

Figure 2. Progression of Neonatal Abstinence Scoring System (NASS) total scores following birth.

birth, weight at birth, or alcohol or cigarette exposure during pregnancy.

For CNS scores, the intercept was significantly associated with both maternal (unstandardized $b = 0.086$, $P < 0.001$) and fetal ($b = -0.088$, $P < 0.001$) antidepressant levels. This indicates that for each 10% increase from the median therapeutic levels in the mother (at birth), the infant's CNS score increased by a significant 0.086. In contrast, the same change in antidepressant level in the infant (at birth) significantly decreased their CNS score by 0.088. No significant relationships were seen with any of the control variables.

No significant relationships were seen between maternal or fetal antidepressant levels and GIT scores (maternal $b = -0.031$, $P = 0.138$; fetal $b = 0.011$, $P = 0.711$) or OTHER scores (maternal $b = 0.007$, $P = 0.539$; fetal $b = -0.004$, $P = 0.731$). A significant effect of smoking during pregnancy on OTHER scores was seen ($b = 0.129$, $P = 0.041$).

Given that the strongest significant relationships were seen with CNS scores, and that the most commonly experienced symptoms in the sample were CNS items (sleep after feeding and tremor), these relationships may in fact be with sleep and/or tremor, rather than the full CNS score. As such, separate growth models for sleep and tremor symptoms were then estimated, and the antidepressant levels entered as predictors.

Both sleep and tremor saw the best fit with intercept-only models of change, and factor scores for those models were estimated. However, although no significant relationships were seen with the tremor intercept, the sleep intercept was significantly associated with both maternal (unstandardized $b = 0.129$, $P < 0.001$) and fetal ($b = -0.131$, $P < 0.001$) antidepressant levels. This indicates that for each 10% increase from the median therapeutic levels in the mother (at birth), the infant's sleep rating increased by 0.129. In contrast, the same change in antidepressant level in the infant (at birth) decreased their NASS sleep rating by 0.131. No significant relationships were seen with any of the control variables.

To assess the clinical significance of this relationship, the sample was grouped by whether their sleep rating was significantly different from zero. By using this grouping variable as an outcome, the effects of antidepressant exposure on the likelihood of the infant exhibiting sleep symptoms can be assessed. Fetal antidepressant levels did not have a significant effect ($P = 0.085$); in contrast, maternal antidepressant levels resulted in the infant being 64.9% more likely to exhibit significant sleep symptoms (odds ratio: 1.649, $P = 0.020$).

Finally, the relationship between discontinuation symptoms at birth and global development at 6 months was assessed. The NASS total factor score was a significant negative predictor of fine motor control at 6 months ($b = -3.982$, $P = 0.044$). However, when the NASS total score was replaced with the three subscale factor scores (CNS, GIT, and OTHER), there were no significant relationships with fine motor control. This would suggest that there may be some mixture of items from these subscales that is responsible, such that the total score is a better representation of these than the individual subscale scores. There was no significant relationship found between NASS total, CNS, GIT OTHER scores and communication, gross motor problem solving, or personal subscales on the Ages and Stages Questionnaire. For CNS and GIT and total NASS, there was no relationship with communication subscale. There was, however, a significant negative relationship between the OTHER scores and communication ($b = -3.420$, $P = 0.001$). Further details of the nonsignificant associations are in **Supplementary Table S2 online**.

DISCUSSION

The findings of this study suggest that the NASS is a valid and clinically useful way of detecting the core groups of symptoms exhibited by neonates following antidepressant exposure. The findings showed inter-rater agreement on both CNS and GIT symptom scores when a pediatrician compared with a midwife assessed the neonate. Although there was no agreement on OTHER, this was attributable to the variation in ratings of respiratory distress, which may reflect the

differing definition from a pediatrician where the threshold may be higher than that of a midwife. The association between symptoms detected with the NASS and both maternal and fetal blood levels for antidepressants also suggests that the NASS is a valid measure. As most maternity centers have experience and protocols for the administration of the NASS for neonates withdrawing from opiates, this would make this scale a pragmatic choice for also measuring neonates exposed to antidepressants.

This study adds to previous findings on the natural course of discontinuation symptoms (4,24). Specifically, the onset and offset of acute symptoms can occur up to 4–5 days after birth, and that for a quarter will persist for 3 days or more. Given these symptoms included poor feeding, there is a potential that maternal antidepressant treatment may have an impact on the successful establishment of breastfeeding and/or may result in poor early growth and weight gain, and this should be noted within clinical care. A previous study by Lewis *et al.* has found poor growth at 1 month in antidepressant-exposed infants; together, this may suggest the need for clear recommendations and guidelines around increased length of stay and monitoring following birth in babies exposed to antidepressants to ensure feeding (formula or breast) is established and support for optimal infant growth and development (14,25).

The current findings also add to the understanding of the processes driving poor neonatal adaptation symptoms in infants exposed *in utero* to antidepressants. Previous theories range from discontinuation, such as is seen in opiate-exposed babies, serotonin toxicity, such as seen in adults with excess exposure to these agents through to neurobehavioral symptoms, suggesting an impact by exposure on the developing nervous system supported by the noted frequency of neurological symptoms. Furthermore, it is possible that these symptoms represent discontinuation and early neurobehavioral markers rather than one pathway. The current findings support suggestions that neonatal adaptation symptoms represent an early neurobehavioral symptom rather than being a transient discontinuation or toxicity syndrome.

Maternal antidepressant levels were associated with CNS symptoms at birth but also continued to predict fine motor at 6 months of age, and this continuity of impact weighs against a discontinuation or neonatal toxicity model. Previous research has found that length of exposure was associated with increased risk of poor neonatal adaptation; although this was not assessed in this current study, this would support an early neurobehavioral phenomenon rather than transient toxicity or discontinuation (2,26). Furthermore, it should be noted that in the current study, two neonates not exposed to antidepressants before delivery but exposed earlier in pregnancy were symptomatic on the NASS, which is inconsistent with the model of transient toxicity or discontinuation. However, alternatively there is the potential for these observed symptoms to reflect both processes co-occurring. As women taking illicit substances or antipsychotic medication were excluded, alternative exposures are unlikely to account for these infants' symptoms.

Two studies have followed up children who experienced poor neonatal adaptation symptoms after fetal antidepressant exposure to school age (15,16). The first study followed up children exposed to antidepressants who either experienced or did not experience poor neonatal adaptation symptoms up to 2–6 years of age (16). They identified a trend toward lower head circumference, hypotonia, and lower social scale on the Denver Developmental Screening Tool. However, they found no difference between those neonates who exhibited poor neonatal adaptation and those infants who did not on cognitive testing, using a range of measures depending on the age of the child at follow-up.

The second study followed up a group of exposed children and a control group to 4 years of age and assessed children using consistent neurodevelopmental measures across the cohort (15). Within those exposed to antidepressants in pregnancy were neonates who had been earlier reported as exhibiting poor neonatal adaptation across clusters including neurological, gastrointestinal, and respiratory symptoms as well as those exposed but with no neonatal symptoms (2). Follow-up showed that neonates who specifically experienced neurological cluster symptoms shortly after birth had trends to lower scores on Movement ABC balance subscale (15). Poorer motor development in exposed children has been identified in several previous studies (27–29).

Although this current study used only a brief developmental screening instrument at 6 months of age, our findings of poorer fine motor functioning associated with NASS total symptoms builds on findings from previous studies. Together, these findings provide a cautious but useful basis to examine motor development in exposed infants with more robust measures at an older age. Furthermore, the questions of both why some neonates develop poor neonatal adaptation symptoms after exposure, whereas others do not, and why some may also go on to exhibit poorer motor development remain unclear, but they may lie in a genetic vulnerability to exposure and this may also be a useful avenue of future exploration (30).

Given the lack of a specific measure to examine antidepressant exposure symptoms in neonates, this study builds on previous findings by examining specific clusters and individual symptoms identified on NASS rather than simply total scores. CNS symptoms were found to most closely correlate with antidepressant levels, and this is the first study to have examined symptom clusters and individual symptoms in relation to antidepressant levels. Of the CNS items, sleeping soon after feeding was most strongly associated with maternal antidepressant levels. Thus, higher levels of exposure were initially associated with sleepiness in the period after birth. The establishment of the circadian rhythm across infancy is an important milestone; however, the understanding of the influences and pathways affecting this rhythm is still imprecise (31). Although several studies have identified a potential relationship between infant sleep and depression, the underlying mechanisms and direction of this association is not

well understood (32–34). The findings from our study suggest that future examination of intrauterine exposure to antidepressant medication may be useful in understanding the relationship between maternal depression and infant sleep development. In particular, future studies may like to include the follow-up of sleep patterns for exposed infants to older ages.

The strengths of this study include the careful characterization of exposure and symptoms in neonates and the capacity to examine identified symptoms in later infancy. The limitations include the small numbers of women using specific therapeutic agents; hence, all analyses have consisted of inclusion of a variety of SSRI and SNRI antidepressant agents. The small numbers of women on SNRIs made even the comparison of SSRIs and SNRIs not feasible. However, as both these drug classes exert serotonin reuptake inhibition, there is no *a priori* reason to believe that they should differ in their effects on the newborn. A final limitation is the lack of neonatal drug levels beyond delivery.

Previous research has suggested that the NASS symptom pattern and clusters after antidepressant exposure differ from those that the NASS was developed to detect. The current findings continue to support the future development of alternative cutoffs and a method for scoring specific to antidepressant exposure as a focus for future research and recommendations. Although an adapted version has been recently developed, this requires wider validation and replication and needs to be embedded within recommendations around length of monitoring across the days after delivery and follow-up of neonates (6).

Overall, these findings continue to support that poor neonatal adaptation symptoms are associated with pregnancy exposure to antidepressant medication. The current findings suggest that a CNS cluster of symptoms is most likely associated directly with the levels of antidepressants and as such should be an area of focus and follow-up in future research. Our findings lend further weight to clinical guidelines that recommend monitoring and support of mothers and infants following delivery when women have been on antidepressant medication in pregnancy. Although the final question about the relevance of the neonatal symptoms for longer-term outcomes was not fully addressed in this study, these findings support following up neonates into infancy and childhood to examine later development. As this report is part of a longitudinal study designed to follow this cohort into later development, this will form part of the focus of future research.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

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