

REGULAR ARTICLE

Acoustic cry characteristics of infants exposed to methadone during pregnancy

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Keywords

acoustic analysis, cry, infant, methadone, neurobehaviour, outcome

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Received

10 February 2008; revised 31 July 2008; accepted 5 August 2008.

DOI:10.1111/j.1651-2227.2008.01011.x

Abstract

Objective: Infant cry characteristics reflect the neurological and medical status of the infant. This study compared the acoustic cry characteristics of infants born to mothers maintained on methadone during pregnancy with those of infants not exposed to methadone during pregnancy.

Methods: At 42 weeks of post-menstrual age, 89 crying episodes ranging in duration from 1.15 to 1.97 sec were collected from 10 methadone-exposed (ME) and 10 non-methadone-exposed (NE) infants. Cry utterances were analysed acoustically using spectrographic displays and measures of cry utterance duration and fine-grained analyses of the fundamental frequency calculated for each cry.

Results: No between-group differences were found on measures of cry duration or fundamental frequency. However, analyses of frequency perturbation showed that the cry utterances of ME infants were characterized by significantly higher levels of frequency perturbation than the cries of infants not exposed to methadone. These effects largely persisted after statistical control for the confounding effects of other maternal drug use during pregnancy.

Conclusion: The crying behaviour of infants exposed prenatally to the synthetic opiate, methadone, is characterized by higher levels of vocal fold vibratory perturbation than NE infants. These findings suggest the possibility of early, subtle neurological vulnerability in this high-risk group of infants.

INTRODUCTION

There is growing evidence to suggest that drug exposure during pregnancy is associated with elevated neurodevelopmental risks for the infant. These risks include higher rates of prematurity, birth complications, reduced head circumference and disruptions to neurotransmitter systems, all of which may increase a child's susceptibility to later cognitive and behavioural problems (1,2). Furthermore, evidence suggests that these complications can manifest subtly and become cumulative over time (3). One drug for which neurodevelopmental follow-up information is limited, especially with respect to sophisticated and fine-grained outcome measures, is methadone.

Since the 1960s, methadone has been widely used in the treatment of individuals addicted to opiate drugs such as heroin, morphine and codeine (4). Methadone maintenance has also become the treatment of choice for pregnant women with an opiate addiction, despite their exclusion from earlier randomized controlled trials (5-8). Although findings remain mixed regarding the effects of prenatal methadone exposure on foetal and infant development, increasing evidence suggests that methadone-exposed (ME) infants are at an elevated risk of neonatal withdrawal, smaller head circumference, irritability, state dysregulation and poorer quality of movements (9-11). Animal studies also suggest disruptions to neurotransmitter systems and impaired brain growth (12-14). More recently, a volumetric MRI study of 11-year-

old children exposed to opiates and other drugs during pregnancy demonstrated reductions in cerebral volumes within the cortex, hippocampus, amygdala, accumbens, putamen, pallidum and cerebellar white matter (15).

An important marker of neonatal neurological integrity that has been examined across a variety of infant groups is crying behaviour. Because cry represents a combination of respiratory, laryngeal and vocal tract functions, any unusual or deviant cry patterns are likely to reflect poor organization in either parasympathetic or sympathetic strands of the nervous system (16). The most common acoustic features examined in infant crying that correspond to respiratory, laryngeal and vocal tract functions are cry duration, fundamental frequency (F_0) and formant frequencies. See Barr (17) and Soltis (18) for a comprehensive overview of infant cry research.

To date, no studies have examined the neurological integrity of ME infants using early crying behaviour. Thus, the aim of this study was to assess the crying behaviour of a group of ME infants relative to a group of non-methadone-exposed (NE) infants on a range of established cry measures. Based on existing research concerning the general anatomical and physiological characteristics of ME infants, three predictions were made. First, given past research showing that ME infants display poorer quality of movements after birth than NE infants (9,10), we hypothesized that ME infants might also show impaired motor control of the onset and offset of crying. That is, the temporal (i.e. durational)

features of cries would differ from those of NE infants. Secondly, past research indicates that ME infants are physically smaller (e.g. head circumference) than NE infants which may also encompass physical size aspects of vocal anatomy. Based on this research, we predicted that a small vocal anatomy would be reflected acoustically as a high F_0 compared to NE infants. Finally, ME infants are known to be highly irritable and dysregulated (9,11). Acoustically, we expected this would manifest as greater variability in the cry signal, notably F_0 .

METHODS

Sample

Study infants consisted of a sub-sample of 10 (4 female, 6 male) ME and 10 (4 female, 6 male) NE infants from a larger case-control study of the neurological effects of prenatal methadone exposure. All infants were term-born singletons delivered at Christchurch Women's Hospital, Christchurch, New Zealand, between 2004 and 2005. Pregnant women maintained on methadone were recruited in their third pregnancy trimester during antenatal visits that were a mandatory part of their treatment with the Christchurch Alcohol and Drug Service (recruitment rate: 90%). Non-methadone-treated comparison women were randomly identified from hospital delivery bookings over the same period (recruitment rate: 60%). Exclusion criteria for the larger study included foetal alcohol syndrome; congenital abnormalities; HIV and gestational age <32 weeks or birth weight <1500 g. The overall mean methadone dose level prescribed for women in the methadone group was 57.83 ± 25.90 mg/kg. For each trimester, methadone dose levels were as follows: trimester 1 = 52.65 ± 35.02 ; trimester 2 = 59.30 ± 24.77 ; trimester 3 = 61.55 ± 25.83 mg/kg. Maternal pregnancy drug use and infant clinical characteristics are described in Table 1.

Measures

Information about women's daily methadone dose levels throughout pregnancy was collated from hospital and drug service records. Close to birth, mothers were extensively interviewed about their licit (nicotine, alcohol, prescription drugs) and illicit (cannabis, opiates, benzodiazepines, stimulants) drug use during pregnancy. Detailed information about each infant's perinatal course was also collected from clinical notes, hospital databases and maternal interview. At 42 weeks of post-menstrual age, infants underwent a comprehensive neurobehavioural assessment using the Neonatal Network Neurobehavioural Scale (NNNS) (19). This examination was completed by an examiner who was unaware of infant group status. Audiotaped cry samples were collected as part of this assessment. All study procedures and measures received ethical approval by our regional committee. Written informed consent was obtained from all parents or guardians.

Cry recording and acoustic analysis

Cry samples were collected from each infant during Section C (*Unwrap & Supine*) of the NNNS administration procedure which involved the application of a tactile stimulation to the heel of the infant's foot. This stimulation served as the method of cry elicitation. A similar method of cry sampling was employed by Nugent et al. (20). One complete crying episode (i.e. bout) was obtained from each infant in a supine position. All infants were in a quiet, restful state prior to cry recording and no attempts were made to elicit cries at particular phases of the infant's respiratory breath cycle. A crying episode was defined as the total period of continuous crying activity (21). An episode of crying commenced with the first audible cry following tactile stimulation. A lapel microphone (Sony ECM-T145) was positioned approximately 15 cm from the infant's mouth. The microphone was attached to a digital minidisk recorder (Sony M2 N710).

On the basis of each infant's episode of crying, a series of cry utterances were identified. Lester et al. (22) defined a cry utterance as an individual segment of crying that occurs during the expiratory phase of respiration. A cry utterance typically lasted for a period of 500 msec or longer. A total of five cry utterances were considered in the acoustic analysis for each infant. In some cases, less than five cry utterances were produced by an infant. Forty-five cry utterances meeting criteria were collected from the ME infants and 44 from the NE infants. Prior to acoustic analysis, the digital recording of each infant's crying episode was converted to a *wav* file using commercially available software (Acoustica 3.2). Each *wav* file was then imported to a signal-processing system (PRAAT 4.3.12). Cry utterances were then measured using a combination of amplitude-by-time displays and narrow-band spectrographic displays. On the basis of these simultaneous displays, five acoustic measurements were obtained.

Cry duration: Defined as the total time elapsed between the onset and offset of each cry utterance. Cry duration (msec) was measured by superimposing a pair of vertical cursors at the onset and offset of visible acoustic energy of each cry utterance. The average cry duration and corresponding standard deviation was calculated for each group.

Cry F_0 : Defined as the lowest frequency component (in Hz) of the cry utterance. Measurements of F_0 were made manually at 100-msec increments across the duration of each cry utterance and the average F_0 and corresponding standard deviation computed for each group.

F_0 variability: Defined according to (a) the F_0 coefficient of variation and (b) F_0 fluctuation. The coefficient of variation, calculated as the ratio of the F_0 SD divided by the mean F_0 , has been shown to be a useful approach for comparing the variability of differing data sets (23). F_0 fluctuation was determined on the basis of the individual F_0 values collected at 100-msec intervals across each cry utterance. Previous infant cry research has found F_0 fluctuation to be a sensitive measure of the subtle variations in vocal fold vibration (24). Two measures of F_0 fluctuations were calculated: (1) the

Table 1 Maternal drug use during pregnancy and infant clinical characteristics at birth of methadone-exposed and non-methadone-exposed infants

Measure	Methadone-exposed infants (N = 10)	Non-methadone-exposed infants (N = 10)	χ^2/t	p
Maternal licit and illicit drug use during pregnancy				
% Used tobacco	90.0	40.0	5.50	0.02
% Used marijuana	30.0	0.0	3.53	0.06
% Used alcohol	10.0	20.0	0.39	NS
% Used benzodiazepines	20.0	0.0	2.22	NS
% Used stimulants	20.0	0.0	2.22	NS
% Used opiates	0.0	0.0	–	NS
Mean (SD) number of other drugs used in pregnancy	1.70 (1.06)	0.60 (0.84)	2.57	0.02
Infant clinical characteristics				
Mean (SD) gestation (weeks)	39.08 (0.90)	39.09 (1.17)	–0.21	NS
Mean (SD) birth weight (g)	3238.00 (472.98)	3438.00 (442.77)	–0.98	NS
Mean (SD) length (cm)	51.60 (3.31)	52.20 (3.23)	–0.41	NS
Mean (SD) head circumference (cm)	34.80 (1.77)	34.65 (1.25)	0.22	NS
Mean (SD) days in hospital	17.40 (12.41)	2.90 (1.60)	3.66	0.005
Mean (SD) highest Finnegan score	13.20 (2.57)	0.20 (0.63)	15.51	<0.0001
Mean (SD) NNNS stress abstinence score	0.17 (0.09)	0.10 (0.04)	2.28	0.04
Mean (SD) NNNS quality-of-movement score	3.82 (0.15)	4.67 (0.80)	–1.88	0.08
% Neonatal abstinence syndrome*	80.0	0.0	13.33	<0.0001

*An infant was diagnosed with neonatal abstinence syndrome if they obtained three consecutive Finnegan scores > 8.

percentage of F_0 directionality and (2) F_0 fluctuation factor. F_0 directionality is a measure that reflects the number of times F_0 changes direction across a cry utterance (i.e. when the algebraic sign changes direction) (25). F_0 fluctuation factor was defined as the mean difference between the frequencies of adjacent F_0 values divided by the mean frequency, multiplied by 100 (25). The F_0 fluctuation factor formula adapted from Baken (25) is given below:

$$F_0 \text{ fluctuation factor} = \frac{\frac{1}{n-1} \left[\sum_{i=1}^{n-1} |F_i - F_{i+1}| \right]}{\frac{1}{n} \sum_{i=1}^n F_i} \times 100$$

where F_i refer to the individual F_0 values and n refers to the number of F_0 values sampled across each cry utterance.

Statistical analysis

Data analysis was completed in three steps. First, maternal pregnancy drug use and infant clinical characteristics for each group were compared using the independent samples t -test or chi-square statistic depending on the distributional properties of the variables. Second, between-group differences in the cry characteristics of ME and NE infants were examined using generalized estimating equation (GEE) models. This approach takes into account clustered observations arising from the use of repeated outcome measures within subjects. It also allows for a variable number of repeated observations or measures per subject. Third, for those cry variables with a significant bivariate association with methadone status, the above models were extended to adjust for the correlated effects of other drug use, by including a diversity measure of poly-drug use as a covariate. Neonatal

abstinence treatment with morphine was not included as a covariate in this analysis since neurobehavioural and cry assessments were not initiated until babies were deemed clinically stable. Furthermore, comparison of ME babies treated and not treated for neonatal abstinence syndrome showed that the cries of treated babies were more regulated and less variable than those of the untreated ME babies across all measures. Finally, in view of our hypothesis testing approach and the small number of infants in each group, one-tailed tests of significance were used.

RESULTS

Cry duration

As shown in Table 2, the average crying durations for the ME and NE groups were 1.37 and 1.47 sec, respectively. This between-group difference was not statistically significant ($p > 0.05$).

Cry F_0

The average cry F_0 of the ME and NE groups is shown in Table 2. The F_0 of cries produced by the ME group was 504 Hz compared to 500 Hz for the NE group. This difference was not statistically significant ($p > 0.05$).

F_0 variability

The F_0 coefficient of variation values calculated for the ME and NE groups are listed in Table 2. The ME group ($M = 0.19$) showed a clear tendency to higher F_0 variability than the NE group ($M = 0.13$) ($p = 0.05$). Results of the F_0 fluctuation analyses are also listed in Table 2. The average F_0 fluctuation factor for the ME group ($M = 112.9$) was significantly larger compared to the NE group ($M = 76.5$) ($p < 0.05$). A similar result was found for the percentage of F_0 directionality, with the F_0 directionality for the ME group

Table 2 Mean (SD) acoustic cry characteristics of methadone-exposed and non-methadone-exposed infants

Cry measure	Methadone-exposed infants (N = 10)	Non-methadone-exposed infants (N = 10)	p
Utterance duration (sec)	1.37 (0.25)	1.47 (0.22)	NS
F ₀ (Hz)	504.16 (145.70)	500.12 (256.81)	NS
F ₀ coefficient of variation (Hz)	0.19 (0.09)	0.13 (0.05)	0.05
F ₀ fluctuation (Hz)	112.93 (59.40)	76.51 (26.53)	0.04
F ₀ percentage directional change	30.77 (8.64)	23.57 (9.49)	0.03

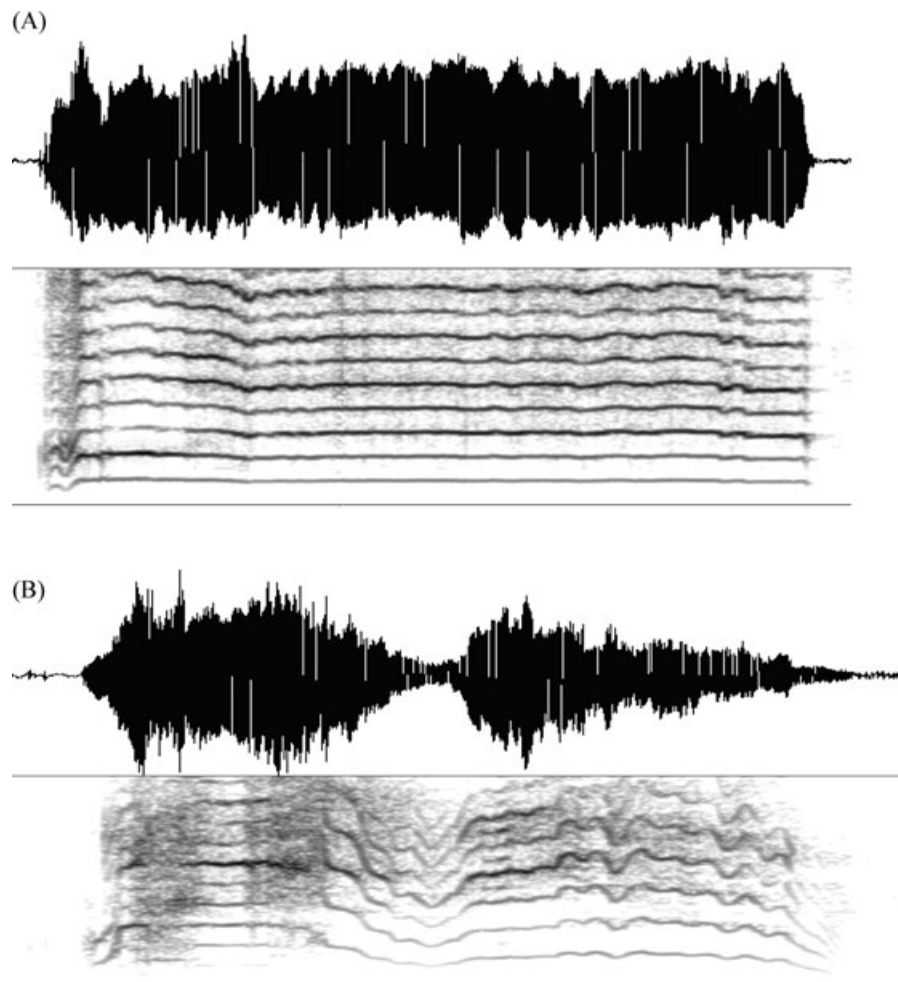


Figure 1 Illustrative cry examples from a non-methadone-exposed infant (A) and a methadone-exposed infant (B). The upper panel for each shows the amplitude-by-time display of the cry whereas the lower panel is a spectrographic (frequency-by-time) display of the same cry. The cry pattern in (A) is one of a stable fundamental frequency (F₀) and the one shown in (B) depicts a highly unstable fundamental frequency (F₀).

(M = 31) being significantly larger than the NE group (M = 24) ($p < 0.05$). An example of the differences in F₀ variability demonstrated by NE and ME infants is illustrated in Figure 1.

Adjustment for the effects of other maternal drug use

Table 3 shows the estimated mean between-group differences and corresponding standard errors, before and after adjustment for the confounding effect of other maternal drug use during pregnancy, for each of the cry outcomes found to

be significant in Table 2. Adjustment for maternal drug use appeared to have had negligible impact on the estimated between-group differences. After adjustment, mean differences between ME and NE infants were unchanged for the F₀ coefficient of variation, increased slightly for the percentage of F₀ directionality and decreased slightly for the measure of F₀ fluctuation. In two cases, the adjusted differences were statistically non-significant ($p = 0.07$ and 0.08). However, this appears to be more a reflection of a slight inflation in the standard error estimates and consequent

Table 3 Differences in acoustic cry characteristics between methadone-exposed and non-methadone-exposed infants, (a) before adjustment and (b) after adjustment for the effects of other maternal licit and illicit drug use during pregnancy.

Cry measure	(a) Mean difference (SE)	p	(b) Mean difference (SE)	p
F ₀ coefficient of variation (Hz)	-0.06 (0.03)	0.05	-0.06 (0.04)	0.07
F ₀ fluctuation (Hz)	-36.42 (20.76)	0.04	-32.67 (24.12)	0.08
F ₀ percentage directional change	-7.20 (3.83)	0.03	-9.59 (4.29)	0.01

reduction in precision of the estimated mean differences following adjustment, rather than any substantive change in the estimated between-group differences. Taken together, these results suggest that the greater acoustic variability in the cries of ME infants was largely unaffected by covariate adjustment and thus could not be explained by the extent of mothers' other licit and illicit drug use during pregnancy.

DISCUSSION

The first hypothesis posed in the present study was that the cry durations of ME infants would be significantly different from NE infants. Past research, as well as the findings of this analysis, reveal poorer quality of movement amongst ME compared to NE infants (9,10). It was anticipated that this impaired motor control might also be reflected in the durational pattern of crying behaviour. However, no such difference was found. Several explanations might account for this finding. First, it is possible that any differences in cry duration that may exist between ME and NE groups may have been too subtle to be detected in this analysis due to limited statistical power. Whilst the sample size used in this study was comparable with other cry studies showing differences between other high-risk infant groups (17,26), a larger sample would clearly have been desirable. Alternatively, it is possible that the poor movement patterns displayed by ME infants are not captured by acoustic measures of cry duration. Past research has used measures of cry duration to infer an infant's respiratory effort and control of phonation (27). Although there is evidence to suggest that ME infants show normal respiratory activity during quiet breathing (28), respiratory activity during crying behaviour has not been assessed. It has been suggested that the sequential timing of muscle activity innervating both the laryngeal and respiratory systems is highly consistent (29). Specifically, electromyographic results indicate that the posterior cricoarytenoid (PCA, a vocal fold abductor) 'activates' prior to diaphragmatic and intercostal muscles during quiet breathing. The early activation of the PCA serves to stiffen the upper airway during moments of inspiration and expiration, thereby helping to avoid airway obstruction (21). It is conceivable that this basic sequence of muscular timing is also evident during moments of phonation. In the case of ME and NE infants, both of whom seem to show normal quiet respiratory activity, the basic sequence of muscular timing related to the onset and offset of cry utterances appears to be similar.

The second hypothesis posed in this study was that the cries of ME infants would be characterized by a higher F₀

compared to NE infants. This hypothesis was motivated by past reports indicating that ME infants tend to be physically smaller at birth than NE infants (9). It was predicted that this size difference might also be reflected in vocal tract anatomy, resulting in a higher cry pitch in ME infants. Based on comparison of various anthropometric features of study infants, there was a tendency, in this small sample, for ME infants to be symmetrically smaller than NE infants; however, these differences did not reach a statistical significance. Similarly, the F₀ of cries produced by ME infants did not differ significantly from the NE infants, although the cries of ME infants were generally higher in F₀ (approximately 14 Hz). These findings suggest that between-group differences in the average F₀ of crying behaviour may be too subtle to offer useful insights into the neurological differences that may separate ME and NE infants.

Whilst measurements of cry duration and average F₀ failed to differentiate ME and NE infants, the various measures of F₀ variability revealed fairly clear between-group differences in crying behaviour. The third hypothesis was developed on the basis of past research noting that ME infants demonstrate poor self-regulation as well as high levels of irritability (9,11). Assuming features of self-regulation also apply to the production of cry, one would expect higher acoustic variability in ME infants compared to NE infants. This was indeed the case for each measure of F₀ variability, including the coefficient of variation, fluctuation factor and directionality. Furthermore, these between-group differences in mean F₀ variability persisted after covariate control for the correlated effects of other maternal drug use during pregnancy.

Grael et al. (24) demonstrated that measures of F₀ variability can be useful for the prediction of developmental outcome. Interestingly, aside from Grauel (24), there has been limited attention paid to F₀ fluctuation in infant crying. It is important to recognize that measures of average F₀ reflect the long-term pattern of vocal fold vibration, that is, the laryngeal activity that encompasses a range of changes in F₀ across a moment of phonatory behaviour, such as a cry utterance. It is the average F₀ that reflects the basic pitch of infant crying, and also serves to differentiate linguistic intent in speech production. On the other hand, measures of F₀ variability reflect 'short-term' (cycle-to-cycle) variations in vocal fold vibration, that is, the fluctuations in laryngeal activity that occur within a single moment of phonatory behaviour. These short-term F₀ variations are thought to be a direct consequence of laryngeal adjustments and reflect automatic (*albeit* subtle) processes of vocal fold vibration (30).

The suggestion that ME infants may differ from NE infants in regard to subtle neurological markers is not new

since a number of studies have linked prenatal exposure to methadone with a range of adverse clinical outcomes. However, extending on this work, our findings also suggest that subtle nervous system differences may also be evident at the level of vocal fold vibration. The extent to which these cry differences are symptomatic of the withdrawal process and thus are potentially transient, or are reflective of more permanent alterations in vocal organization and regulation are yet to be established. Concurrent neurological and neurobehavioural studies, as well as follow-up studies examining the prognostic significance of early infant cry characteristics appear warranted and should help to clarify this issue. Nonetheless, our results do offer an acoustic profile of the crying behaviour of ME infants and highlight the possibility of subtle neurological vulnerability in these infants.

ACKNOWLEDGEMENTS

This research was funded by a grant from the New Zealand Lottery Grants Board and a postgraduate scholarship from the University of Canterbury. We are also grateful to Carole Spencer and Verena Kreiliger for sample recruitment and data collection assistance, John Horwood for biostatistical advice and most importantly, study families for supporting this research.

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