

Maternal sounds elicit lower heart rate in preterm newborns in the first month of life



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ABSTRACT

Background: The preferential response to mother's voice in the fetus and term newborn is well documented. However, the response of preterm neonates is not well understood and more difficult to interpret due to the intensive clinical care and range of medical complications.

Aim: This study examined the physiological response to maternal sounds and its sustainability in the first month of life in infants born very prematurely.

Methods: Heart rate changes were monitored in 20 hospitalized preterm infants born between 25 and 32 weeks of gestation during 30-minute exposure vs. non-exposure periods of recorded maternal sounds played inside the incubator. A total of 13,680 min of HR data was sampled throughout the first month of life during gavage feeds with and without exposure to maternal sounds.

Results: During exposure periods, infants had significantly lower heart rate compared to matched periods of care without exposure on the same day ($p < .0001$). This effect was observed in all infants, across the first month of life, irrespective of day of life, gestational age at birth, birth weight, age at testing, Apgar score, caffeine therapy, and requirement for respiratory support. No adverse effects were observed.

Conclusion: Preterm newborns responded to maternal sounds with decreased heart rate throughout the first month of life. It is possible that maternal sounds improve autonomic stability and provide a more relaxing environment for this population of newborns. Further studies are needed to determine the therapeutic implications of maternal sound exposure for optimizing care practices and developmental outcomes.

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1. Introduction

The fetus has a substantial capacity for sound recognition and auditory learning in the intra-uterine environment [1]. As an indication of this, newborn infants show a clear preference for their mother's voice shortly after birth [2,3]. The fetus, however, does not begin its auditory experience by hearing sounds, but rather by sensing them through the bones of the skull [4]. Hearing begins at approximately 25–26 weeks of gestational age (GA) as cochlear hair cells first translate acoustic vibrations and then airborne sound stimulation into coded electrical signals that are sent to the brainstem for additional processing [5]. Consistent responses to vibroacoustic stimuli have been observed in the fetus from approximately 27–28 weeks onwards [6], particularly in response to low frequency sounds [7]. These basic auditory skills are known to be a prerequisite for subsequent processing of human speech sounds, beginning with mother's voice.

Fetal response to mother's voice has been mainly identified by measuring heart rate (HR) changes. This response, beginning at 32 weeks of gestational age (GA), has been robustly demonstrated by Kisilevsky and colleagues [8]. Over two minutes of voice exposure, fetuses from 32 to 37 weeks of GA showed an initial HR decrease for 30 s, followed by a HR increase until the end of the stimulus. By the time fetuses reached term age, however, the response shifted to an immediate HR increase which was sustained for the full 2 min of voice exposure [9]. Overall, fetal HR at near-term has been shown to increase in response to the mother's voice and decrease in response to a stranger's voice [10]. Studies have suggested that this preferential response is modulated by HR variability and cardiac vagal tone, reflecting a pre-attentional form of reaction [11]. The neural basis of this response was recently revealed using fMRI in normal pregnancy fetuses at 33–34 weeks' gestation [12].

Pregnancy complications and atypical prenatal development can significantly restrict auditory recognition abilities, dampening the perception of sounds in utero. For example, iron-deficient infants born to diabetic mothers [13] demonstrated shorter event-related potentials (ERP) in response to acoustic stimulation of their mother's voice. Similarly, growth-restricted fetuses and newborns showed significantly

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weaker HR response to their mother's voice compared to healthy controls who were appropriately grown for gestational age [14]. Thus, the integrity of the intra-utero environment seems to be important for securing optimal auditory development.

The prenatal response to mother's voice continues postnatally. Term newborns show perceptual sensitivities in response to familiar speech stimuli [15]. This preferential response has been demonstrated in full-term infants by several measurements, including increased non-nutritive sucking [16] and reactive movement towards the source of the sound [17]. Interestingly, newborn infants also show a preference to the type of language used (i.e., native vs. foreign) based on their individual language experience in utero [18,19]. Most recently, Beauchemin and colleagues showed that exposure to maternal voice activated language-related cortical areas, whereas a stranger's voice activated more generic voice-specific areas [20]. The authors interpreted their findings as evidence for an innate auditory-motor speech loop, specifically tailored to the mother's voice. Similarly, Partanen and colleagues [21] demonstrated that term newborns react differentially to familiar vs. unfamiliar sounds they were exposed to as fetuses, revealing a direct correlation between the amount of prenatal exposure and brain activity. The above studies suggest that auditory attention, learning, and memory originate before birth to allow proper priming of language centers of the brain.

Whereas the newborn and fetal response to mother's voice has been well studied, the sustainability of this response following a premature birth is not fully understood. Chronologically, a typically-developing fetus at 28 weeks of gestation and an infant born 12 weeks prematurely are exactly of the same age; however, developmentally, they may show very different HR responses when presented with their mother's voice. The ability of preterm newborns to show a preference for their mother's voice while still in the Neonatal Intensive Care Unit (NICU) may be constrained by several factors including their immature nervous system, their hypersensitivity to loud noise, the sudden demands for hearing through air (instead of amniotic fluid), and their limited capacity to hear human speech sounds clearly in the noisy NICU environment. Thus, it is unclear whether HR changes observed in preterm infants are solely indicative of their physiological response to mother's voice or possibly a reflection of cardiorespiratory instability or side-effects of caffeine treatment [22].

A number of studies have examined the impact of maternal voice in the preterm population (for review see [23]); however, only a few studies have specifically utilized HR analysis to measure the infant's response. An early study identified decreased HR in this population with exposure to maternal voice compared to white noise [24]. Recent studies have identified increased HR in response to live maternal speech [25], but no difference in response to recorded maternal speech [26]. However, the response of preterm infants to recordings which include both mother's voice and heartbeat in an attempt to simulate the intra utero environment has not yet been studied. Additionally, the nature of this response in the first critical month of life and the extent to which it might be affected by the infant's age, health status, respiratory support, and caffeine therapy remain unstudied and would be an important contribution to our current understanding. The present study aimed to fill these gaps in knowledge by examining the effects of exposure to mother's voice on HR in hospitalized preterm newborns in the first month of life. It was hypothesized that exposure to mother's voice and heartbeat would result in decreased HR compared to matched periods of care without exposure on the same day.

2. Methods

2.1. Study population

Twenty preterm infants participated in this study. The study was approved by the Institutional Review Board (IRB), and parents gave written informed consent within approximately the first week of life.

Table 1 Population Characteristics.

Total subjects	20
Female sex, %	35
Maternal age (y) ^a	33 ± 5.6 (18–42)
GA at birth (wks) ^a	29 ± 2.4 (25 5/7–32 4/7)
Birth weight (g) ^a	1231 ± 302.4 (700–1710)
Apgar 5 min ^a	8 ± 1.1 (6–9)
PMA at study onset (wks) ^a	30 ± 2.5 (26 2/7–33 4/7)
Required respiratory support attesting, %	63
Full gavage feeding at testing %	75
Caffeine treatment, % ^b	90

^a Values are shown as Mean ± SD (range).

^b Average dose of 6.38 mg/kg/day in the first month of life.

The mean gestational age at birth was 29 weeks ($SD = 2.4$) and the mean post menstrual age (PMA) at study onset was 30 weeks ($SD = 2.5$). A detailed description of the study population is given in Table 1. Inclusion criteria included: birth GA between 25 and 32 weeks. Exclusion criteria included: chromosomal anomalies;; major congenital anomalies; symptomatic infections; congenital hearing loss; perinatal brain lesions; small for gestational age; anemia of prematurity ($Hgb \leq 10$ g/dL); history of significant maternal deprivation, abuse or malnutrition; history of maternal alcoholism or use of illicit drugs; and smoking during pregnancy in light of evidence for impaired auditory discrimination of speech sounds in infants of smokers mothers [27]. All infants passed their hearing test prior to NICU discharge.

2.2. Maternal sound recording

Mother's voice and heartbeat were recorded individually for each infant in a specialized recording studio. Voice recording was done in a standardized fashion via a large-diaphragm condenser microphone (KSM44, Shure, USA), capturing three types of vocalizations (speaking, reading, and singing) from each mother. The maternal recordings were attenuated using a low-pass filter with a cutoff of 400 Hz, and were subsequently mixed with individualized recording of the mother's heartbeat via a digital stethoscope (ds32a, Thinklabs Digital Stethoscopes, USA). The maternal voice was overlaid with the recording of the maternal heartbeat so that the infant could hear them simultaneously. This was done in an attempt to simulate the auditory experience in utero. The maternal recordings were loaded onto an MP3 player (Phillips Electronics, SA2RGA04KS, Netherlands) for playback via microaudio speakers at the bedside. Maternal sounds were played at a mean LAeq of 57.2 ± 3.4 dBA (A-weighted). Loud peaks were attenuated to achieve a safe level of sound delivery <65 dBA to approximate normal human conversation [28] as would otherwise occur when a mother speaks to her infant at the bedside. This sound attenuation protocol was administered individually for each infant by a sound level meter (Bruel & Kjaer, 2250, Denmark) as validated in a previous safety and feasibility study [29] and was successfully used in recent studies from our group [30,31].

2.3. Study procedure

Nurses were instructed to coordinate the maternal sounds with the infant's routine care, 4×/day, avoiding playing the sounds during parental visits and clinical exams. The exact time maternal sounds were played was denoted by nurses on a study timesheet at the bedside. Maternal sounds were always played after the care session, when the infant was tucked in and put to sleep, as gavage feeding was initiated. HR data was collected from the infants' cardiac monitor four times a day, twice a week, over a 30-minute period during two feeds *with* and two feeds *without* exposure to maternal sounds on the same day. This approach allowed us to compare the infant's HR during clinically-comparable periods in the infant's NICU routines, resulting in a total of 24 data collection sessions per infant throughout the first month of life. Analysis was based on 13,680 min of data, with 720 data points per infant (three infants had missing data contributing 480 data points

each). Cardiac monitor data was obtained at a sample rate of 1 min and measured as beats per minute (bpm).

2.4. Statistical analysis

HR data was averaged across the 30-minute data collection sessions, resulting in 24 mean HR values per infant. Mean HR and sound condition (exposure vs. non-exposure to maternal sound) were then analyzed using a linear mixed model with subject treated as a random effect. The intercepts for the subjects were allowed to vary to take into account the within-subject correlation of the HR. A sound \times respiratory support interaction was tested to investigate whether the effect of maternal sound varied by presence of respiratory support. A sound \times caffeine therapy interaction was tested to investigate whether the effect of maternal sound varied by caffeine therapy. To investigate whether the effect of maternal sound varied by day-of-life a maternal sound \times day-of-life interaction was tested. Post-hoc pairwise comparisons were used to compare the mean rates in the four sound \times respiratory support conditions and in the four sound \times caffeine therapy conditions. As these comparisons were few and pre-planned, p -values are presented without adjustment for multiple comparisons. The magnitude of HR response to maternal sound was computed for each baby from the difference between mean HR with and without maternal sound. Pearson correlations were then computed to determine the relationship between the magnitude of HR response and infant characteristics (birth GA, birth weight, Apgar scores, PMA). Statistical analysis was performed with IBM SPSS 22 and Graphpad Prism 6. p -Values less than 0.05 were considered statistically significant.

3. Results

During exposure to maternal sounds, infants had significantly lower HR (158.9 bpm) compared to matched periods of care without exposure on the same day (162.9 bpm) ($p < .0001$; Fig. 1A). This effect of maternal sounds on HR was demonstrated by all study infants (Fig. 1B), and was not affected by day of life ($p = 0.354$; Fig. 1C).

Infants had consistently lower HR in response to maternal sounds compared to routine hospital sounds both on respiratory support (158.1 vs. 162.2 bpm, $p < .0001$) and when breathing room air (160.1 vs. 163.6 bpm, $p < .006$) (Fig. 2A). In addition, infants had consistently lower HR in response to maternal sounds compared to routine hospital sounds both while on caffeine therapy (159.4 vs. 163.2 bpm, $p < .0001$) and off caffeine therapy (156.4 vs. 160.7 bpm, $p = .034$) (Fig. 2B). Interactions between sound condition and respiratory support/caffeine therapy were not significant, indicating that the magnitude of the effect of maternal sounds was similar whether or not these two therapies were in use.

Pearson's correlations indicated no relationship between infant characteristics and the magnitude of HR response to maternal sounds (see Table 2). The magnitude of HR response was determined by the difference between mean HR without and with maternal sounds.

4. Discussion

This study demonstrated a differential response in hospitalized preterm infants when listening to maternal sounds. Infants showed sustained mean HR decrease during repeated 30-minute periods of recorded maternal sound exposure. This effect was consistently observed in all infants participating in the study throughout the first month of life, irrespective of day of life, gestational age at birth, birth weight, Apgar scores, caffeine therapy, or respiratory support. Thus, despite medical vulnerability and individual variability, preterm infants respond with distinct HR changes to audio recordings of their mother's voice. The results may be cautiously interpreted as a relaxation response to maternal sounds and as such, possible clinical implications should be further examined.

The physiological response of preterm infants to their mother's voice observed in our study is consistent with previous studies in the fetus [32]. This similarity is not surprising given that preterm infants are of the same gestational age as late-stage fetuses. However, it is important to highlight that the measurements window used in our study is noticeably different than those used in the fetal studies. Majority of fetal studies have focused on the instant reaction of the fetus to short sound bursts, ranging from 2s to 2 min, including both speech [8–10] and non-speech [33] stimuli. This immediate reaction reflects an abrupt shift to a more attentive state often indicative of an orienting response. In contrast, the present study analyzed the infant's response over a period of 30 min, and thus our findings of significantly lowered HR should not be interpreted as an orienting response, but rather as a possible systemic reaction that may affect relaxation and autonomic stability. Other relaxation techniques, such as various types of infant massage [34], have been shown to provide comfort in the stressful environment of the NICU. However, maternal sounds may offer an earlier opportunity for sensory enrichment, as early as 26 weeks, when auditory stimulation is developmentally appropriate and tactile stimulation is often avoided due to medical instability.

The results of the present study demonstrate the capacity of preterm infants to perceive and respond to sound stimuli in the NICU environment. The NICU environment includes both optimal and suboptimal stimuli. Whereas exposure to stressful stimuli, such as loud noise, can increase HR [35] and adversely interfere with behavioral-sleep states [36], soothing auditory stimuli, such as maternal sounds, can hypothetically yield a more positive response. Our results are in keeping with previous studies demonstrating improved relaxation and attentive states [26], improved cardiorespiratory stability [30], reduced HR [24], reduced episodes of feeding intolerance [37], and improved growth velocity [31] in preterm infants receiving maternal sound exposure. It is therefore possible that mother's voice can be a positive stimulus and further studies are necessary to understand the extent to which it promotes healthy development in preterm infants. Given the small sample size, results of this study should be considered with caution and effect size may be limited.

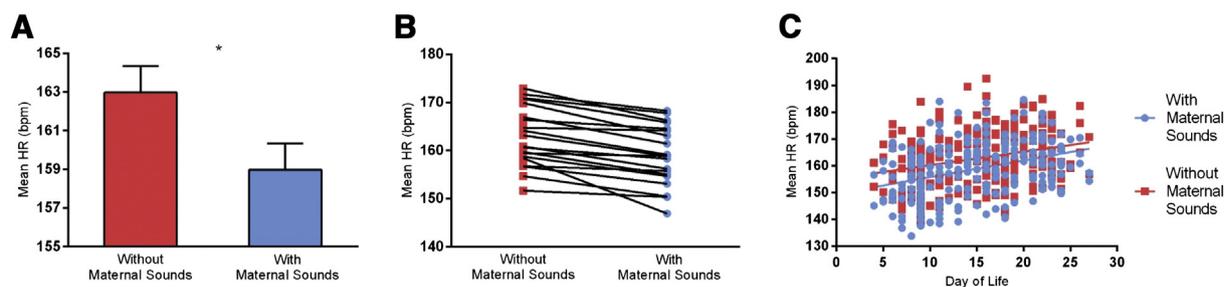


Fig. 1. Mean HR response to maternal sound exposure. Shown are mean HR during 30-minute exposure vs. non-exposure periods of recorded maternal sounds played inside the incubator. HR data sampled throughout the first month of life during gavage feeds with and without exposure to maternal sounds. (A) During exposure periods, infants had significantly lower heart rate compared to matched periods of care without exposure ($p < .0001$). (B) Mean HR is shown for each individual infant. Maternal sounds elicited lower HR as demonstrated by all study infants. (C) The response to maternal sounds was not affected by the infant's day of life as indicated by parallel trend lines with (blue) and without (red) exposure ($p = 0.354$).

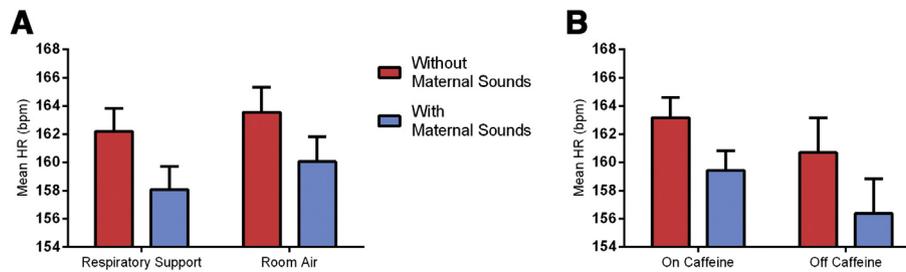


Fig. 2. Effects of respiratory support and caffeine therapy on mean HR response to maternal sound exposure. Post-hoc pairwise comparisons show that infants had significantly lower mean HR during exposure to maternal sounds compared to matched periods of care without exposure regardless of whether they were (A) on respiratory support (158.1 vs. 162.2 bpm, $p < .0001$) or breathing room air (160.1 vs. 163.6 bpm, $p < .006$); and (B) on caffeine therapy (159.4 vs. 163.2 bpm, $p < .0001$) or off caffeine therapy (156.4 vs. 160.7 bpm, $p = .034$).

It is striking that decreased HR was observed in each individual infant exposed to maternal sounds, with a mean HR decrease of 4 bpm across the cohort, regardless of respiratory support and caffeine therapy. However, it remains unclear whether the HR effect of 4 bpm observed in the present study is clinically significant and to what extent the effect would have changed with longer periods of exposure to mother's voice and/or a larger sample size. Although the direct effect of decreased HR on health outcomes in hospitalized preterm infants is not fully established, the common impression is that sustained decreases in HR are indicative of infant focused attention and may increase the overall potential for cognitive development [38]. These findings are especially interesting given that high peaks of HR have been correlated with poor health in the preterm population (e.g., sepsis, NEC, and acute respiratory deterioration) [39], whereas lower HR has been correlated with improved behavioral regulation and social skills at three years of age [40]. Our findings demonstrate that repeated exposure to maternal sounds can be well coordinated with routine care practices and be effectively administered to achieve sustained decrease in HR in the first critical month of life. Albeit encouraging, the results of the present study require further investigation to determine the optimal combination of maternal sound exposure, respiratory settings, and caffeine dose in preterm infants.

Although our results indicate that the effect of maternal sounds on HR was independent of gestational age at birth, the extent to which age can modulate the preterm infant's response to mother's voice is still unclear and studies have reported mixed results. This might be attributed to the range of variability across studies in stimulus type, duration, and intensity (for review see [23]). A study involving both full-term and preterm newborns found a significant correlation between postconceptional age and the maturation of recognition of maternal voice [41]. Another study found correlation between the amount of prenatal auditory exposure in utero and the degree of mismatch responses to pitch changes after birth [21]. The present study, however, was not designed to examine the age onset of maternal voice recognition and, thus, no firm conclusions can be drawn. Our results suggest that overall, the basic effect of maternal sound exposure on HR does not depend on birth GA, day of life, or PMA.

It is important to acknowledge the difference between live vs. recorded maternal voice. Unlike the repetitive and artificial nature of recorded maternal sounds, live speech provides the infant with a more variable and realistic type of stimulation, which may prevent habituation and increase opportunities for learning. In addition, live exposure to maternal voice can naturally be incorporated with skin-to-skin care

practices. While the benefit to having the mother physically present is unquestionable, in reality, however, it is often unfeasible for mothers to remain at the bedside all day, in which case, the use of recorded maternal voice may provide a valuable supplement. Previous research examining the effects of live maternal sounds in preterm infants have reported mixed results, including both decreases [42], increases [25] or no change [26] in HR. However, the response to recorded sound stimuli, like in our study, is in keeping with previous research showing reduced HR in response to recorded vocal music [43] and parent-preferred lullabies [44]. Future research is necessary to establish the most optimal way of delivering maternal sound stimulation in the NICU.

A unique aspect of our study is the simultaneous inclusion of both the maternal heartbeat and the maternal voice recordings on one audio track. Overlaying the mother's voice with a recording of her heartbeat allowed us to produce a more authentic simulation of the auditory environment the infant would otherwise be hearing in the womb. However, this stimulus composition may also be considered a study limitation for the way in which it prevents us from teasing apart which component of the maternal sound stimulus generated the observed response. Considering the presence of competing acoustic signals in the NICU environment, better approximation of the signal-to-noise ratio inside the incubator such as demonstrated by Kuhn and colleagues [45] would be necessary to determine the relative contribution of each of the stimulus components. Thus, at this stage it remains speculative if preterm infants can be more soothed by solely their mother's voice, her heart beat or a synthesized combination of the two.

Finally, in addition to promoting relaxation, exposure to maternal sounds may provide preterm infants with the necessary language exposure for the development of future speech and language abilities. Limited linguistic stimulation in the neonatal period is thought to hinder language and cognitive development [46]. Thus, repeated exposure to maternal sounds provides a continuation of the prenatal exposure to maternal speech that may lay the foundation for later language development. Our finding that exposure to maternal sounds lowered HR in this vulnerable population opens the door for considering remodeling the NICU environment to incorporate more maternal sounds since they are likely to increase linguistic opportunities. The potential use of maternal sounds for promoting therapeutic relaxation and language development warrants further investigation.

5. Conclusions

The results of this study add to a growing body of literature that supports both the feasibility and the potential benefits of maternal sound exposure for improving health outcomes of premature infants. The existence of consistently decreased HR in response to maternal sounds encourages the integration of this presumably soothing stimulus into routine care practices. This may be especially beneficial in helping preterm infants achieve physiological comfort, while providing their brain with the necessary stimulation for optimal auditory and language

Table 2 Correlations between infant characteristics and magnitude of HR response.

Measure	r	p
Birth GA	0.178	0.453
Birth weight	-0.082	0.732
Appgar 5'	0.088	0.712
PMA	-0.081	0.394

development. To test this hypothesis and extend the findings of this study, future research should focus more specifically on determining the therapeutic implications of maternal sound exposure for optimizing autonomic and homeostatic regulation in the preterm population.

Conflict of interest statement

The authors have no conflict of interest to report.

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