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REVIEW

Effect of music therapy in preterm infants

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ABSTRACT

Music therapy has been recognized as a supportive intervention for the neurosensory and cognitive development of both full-term and preterm newborns. The objective of this article is to provide an updated overview of the use of music therapy in preterm infants and to discuss the potential neurological pathways through which this technique may affect the vital parameters of these infants.

Studies were selected based on outcomes measured with electromedical equipment. A total of 12 studies were identified: 1 cross-sectional survey, 6 randomized controlled trials (RCTs), and 5 reviews. The 5 reviews, which analyzed 232 trials, consistently reported positive effects of music therapy on the basic vital functions of infants, such as heart rate (HR), respiratory rate (RR), oxygen saturation, feeding, and length of hospital stay.

The neural and humoral interactions stimulated by music therapy in infants may explain the improvement in their basic vital functions during and after sessions, resulting from the relaxing music programmed by the music therapist.

IMPACT STATEMENT: Music therapy positively influences preterm infants' vital functions, including heart rate, respiratory rate, and oxygen saturation, by stimulating neural and humoral pathways. This article highlights its potential as an effective intervention for supporting neonatal development and reducing hospital stays.

KEY WORDS

Pre-term infant; neonatal intensive care unit; music-therapy.

INTRODUCTION

'Preterm birth' refers to infants born before 37 weeks of gestation and is categorized by gestational age into three subgroups: extremely preterm (less than 28 weeks), very preterm (28 to less than 32 weeks), and moderate to late preterm (32 to 37 weeks). In 2020, an estimated 13.4 million babies were born prematurely, representing more than 1 in 10 births globally (1). According to a recent UNICEF report, 10.6% of all births are preterm, leading to approximately 3.1 million deaths worldwide (2). Many of the survivors face lifelong challenges, including cognitive disabilities, as well as visual and hearing impairments. In developed countries, preterm births are relatively common, partly due to declining birth rates and the difficulties some couples encounter with conception. In some of these countries preterm birth rates have been reported to range from 5% to 7% of live births, but these rates are likely underestimates and appear to be increasing (3).

Premature infants, with underdeveloped vascular and neurological systems, are abruptly transitioned from the protective environment of the womb into the unprotected world of the Neonatal Intensive Care Unit (NICU). They are often unable to manage many of the stimuli essential for sustaining life. This environment exposes them to bright lights, loud sounds, physical touch, and other unfamiliar stressors (4). Each of these stimuli can be perceived as a source of stress by the immature nervous system of a premature infant, potentially leading to impaired oxygenation, altered blood flow, abnormal heart rate, and adverse behavioral responses (5). Additionally, damage to the auditory system can result from harmful stimuli in the environment, such as ototoxic medications and excessive noise (6). Cochlear hair cells can lose their sensitivity to pitch when exposed to background sound levels of 60 decibels (dB) or higher (7). To help prevent hearing damage or hearing loss in infants hospitalized in the NICU, the American Academy of Pediatrics (AAP) has recommended keeping noise levels below 45 dB. However, a quiet room typically measures around 47 dB, and the advanced technological equipment used to care for premature infants in the NICU often exceeds these guidelines. The elevated noise levels associated with routine care for preterm infants may put them at risk of auditory system damage and instability in their basic vital functions (8).

Music is a combination of sounds organized according to melody, harmony, and rhythm, which are perceived and processed by the human brain (9). Music therapy involves the use of sound and music with the aim of achieving specific therapeutic goals (*e.g.*, reducing stress) that contribute to the improvement of the patient's clinical condition (10). Music therapy has been recognized as beneficial for the neurosensory and cognitive development of both full-term and preterm newborns (11). Studies on its effects are often conducted on hospitalized children, making preterm infants particularly suitable for such analysis, as they remain monitored in Grow Care Units or in NICU for extended periods − ranging from weeks to months − until they reach the vital parameters needed to survive without medical assistance (12).

The aim of this study is to provide an updated overview of the use of music therapy in preterm infants and to explore the potential neurological pathways involved in its influence on their vital parameters.

METHODS

PubMed, Embase, and Cochrane databases were utilized to identify the most relevant studies conducted over the past 20 years (from 2004 to 2024). Additional scientific papers were included as they appeared in the selected articles. The selection of papers for analysis followed the PRISMA guidelines (13).

For the search we utilized the following keywords: 'preterm infants', 'music therapy', and 'intensive care unit', focusing on objective data related to heart rate (HR), respiratory rate (RR), and oxygen saturation, outcomes objectively measurable with electro-medical equipment. Papers addressing topics such as parent-infant bonding, effects on mothers, pain, and long-term developmental outcomes were excluded

The selected articles met the following criteria:

– published in peer-reviewed scientific medical journals in English;
– article types: randomized controlled trials, reviews, and systematic reviews.

The analysis presented in this paper is narrative, and no meta-analysis was conducted.

RESULTS

A total of 42 papers initially met the selection criteria. An additional 2 papers were included from citations found within the reports, bringing the total to 44. Of these, 30 reports were excluded from the selection for not meeting the inclusion criteria, or because their outcomes could not be objectively measured with electro-medical equipment. Additionally, 2 papers were deemed irrelevant by the two reviewers (FB and AB).

Thus, 12 studies were selected for this review. The selection criteria are detailed in the flowchart (**Figure 1**), following PRISMA guidelines (13), and the studies are listed in **Table 1** (14-25) based on publication date. Notably, the systematic review by Costa S.V. *et al*., which included 39 studies, and the paper by Mohan A. *et al*., which analyzed results from 12 systematic reviews, 14 randomized trials, and 7 observational studies, led to the exclusion of numerous duplicates from the initial selection.

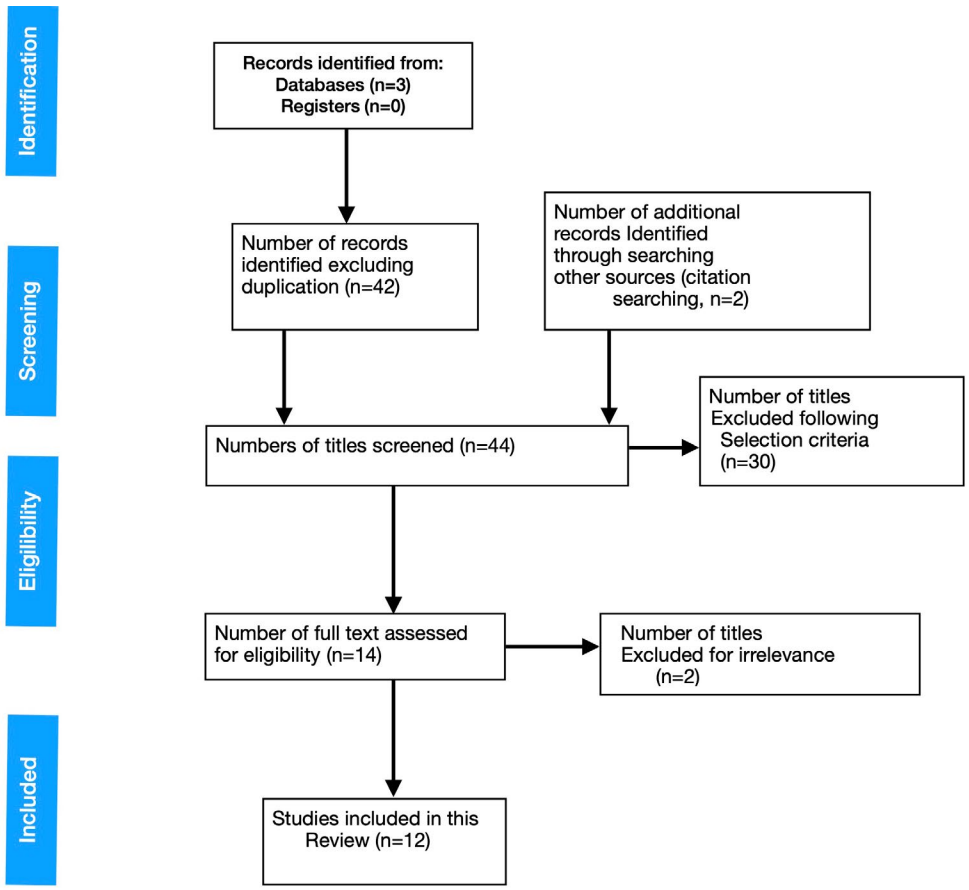

Figure 1. *PRISMA flow chart for papers' inclusion.*

The papers studied in our review included 1 cross-sectional survey, 6 randomized controlled trials (RCTs), and 5 reviews. The cross-sectional survey (1) involved a NICU staff with the administration of questionnaires evaluating the effects of music on infants and staff members. The feedback from medical and nursing staff indicated a highly positive impact of music therapy on the small patients.

The total number of preterm infants studied in the 6 randomized controlled trials (RCTs) is 268. Among these, study 5 examines cardiac function through continuous ECG to assess heart rate variability. This study suggests that music therapy, influencing subcortical and cortical brain stimulation, may have a positive effect on cardiac function in preterm infants.

Study 12 evaluates the impact of music therapy on preterm infants during their hospitalization by assessing the integrity of the brain's white matter through MRI. Results indicate a positive increase in white matter integrity in infants who received music therapy compared to controls.

Among the remaining 4 RCTs, study 2 reports no significant changes in basic physiological functions such as heart rate (HR), respiratory rate (RR), and oxygen saturation between preterm infants receiving music therapy and those in the control group. Conversely, studies 3, 4, and 7 demonstrate improvements of these parameters: study 3 and 4 show enhanced oxygen saturation in infants during the music therapy sessions, particularly when the mother is present; instead study 7 indicates a reduction in HR and RR, along with increased oxygen saturation during sleep over the course of music therapy. Study 8 assesses EEG variations during sleep in infants undergoing music therapy, revealing improvements in EEG patterns during sleep.

Table 1. *RCT, Systematic Reviews and a survey included in this study.*

N. (ref.)	First Author	Year	Type of paper	Number of participants	Type of music (dB)	Duration of music therapy (dB when reported)	Outcomes
1.-(14)	Kemper K.	2004	Cross sectional survey of NICU staff	37 physicians and 150 nurses for a total of 187 questionnaires	Recorded music (but preferred live music)	Winter 2023: Music continuously played in NICU	Staff reported in preterm infants <Stress <Crying >Sleep
2.-(15)	Alipour Z.	2013	RCT	90 premature infants: G1-30 lullabies G2-30 silence CG-30 control	Lullabies played by headphones	Each session of 20 minutes lullaby treatment (50-60 dB) per day or silence	No effects on HR, RR, oxygen saturation immediately and 10 minutes after each session
3.-(16)	Dearn T.	2014	RCT	22 preterm infants born at >28 wg and enrolled at >32 wg (+/- their mothers): 10 Study Group = SG 12 Control Group = CG	Listen to recorded lullabies and ambient sound	6 minutes of ambient sound alternating with 2x6 minutes recorded lullaby music	SG > oxygen saturation (pre-term with mother present) than CG
4.-(17)	O' Toole A.	2017	Review	N. 12 papers in the previous 5 years in pre-term infants	Different types of music, and parental involvement	Receptive MT	<HR <RR >Oxygen saturation >Feeding >Length of stay >Pain relief <Parental stress
5.-(18)	Hasegawa Y.	2020	RCT	N. 30 pre-term infants	Lullabies for a baby, delivered through a speaker in the incubator	Evaluation of HR variability before, during and after each intervention	LF and HF values decreased during the MT condition, but not LF/HF
6.-(19)	Mohan A.	2021	Systematic reviews and meta-analysis of RCTs	- 12 systematic reviews - 14 RCT - 7 observational studies	Different types of music (lullabies, recorded music, *et al*.)	Different musical approach	<HR <RR <Maternal anxiety >Feeding volume
7.-(20)	Kobus S.	2021	RCT	20 (<32 wg) Tot.: 307 MT sessions	Improvised singing / use of sansula instrument	2 individual music session per week (from 2 week of life until discharged).	<HR <RR >Oxygen saturation better during sleep
8.-(21)	Giordano V.	2021	RCT	64 (in 3 groups: G1 = live music G = 2 recorded music group G3 = control group	Live or recorded music	Amplitude-integrated EEG, 20 min after the appearance of the first quiet-sleep phase	Improvement within the first and second quiet-sleep epochs in G1 and G2
9.-(22)	Yue W.	2021	Systematic review of trials and meta-analysis	13 trials involving 1,093 participants	Music therapy with recorded music or music obtained with different techniques and/or instruments	Music sessions 1 or more times a week	<HR <RR >Oral feeding volume

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N. (ref.)	First Author	Year	Type of paper	Number of participants	Type of music (dB)	Duration of music therapy (dB when reported)	Outcomes
10.-(23)	Costa V. S.	2022	Review	39 trials, 13 on analgesic effect and 26 evaluated the physiological and behavioral effects of music (977 participants).	Recorded music or lullaby, live music with instruments (harp) or lullaby and parents' song.	In 3 RCTs the MT session was single, in the other each MT session lasted from 10' to 60' 2-3 times a week, until discharge from the hospital (30-70 dB)	>Pain relief <HR <RR >Oxygen saturation >Weight gain and eating behavior
11.-(24)	Haslebeck F. B.	2023	Systematic review	25 trials, recruiting 1532 infants and 691 parents	Music and voice were calm, soft, in lullaby style, and the mother's voice live or recorded	Different musical approach	During MT session: - stable oxygen sat - stable RR - <HR during and post each MT session
12.-(25)	Dewan M. V.	2024	RCT	80 infants enrolled, 42 were eligible for diffusion tensor imaging analysis (MT22 = G1; ST20 = CG)	Live MT (LM)	LM was provided twice weekly from the second postnatal week onwards by a trained music therapist	>Effect of MT on white matter microstructures on cranial RMN scan, between G1 and CG

MT: Music Therapy; RCT: Randomized Controlled Trial; G 1-2: Groups of Patients; CG: Control Group; SG: Study Group; HR: Heart Rate; RR: Respiratory Rate; EEG: Electroencephalography; LF: Low Heart Frequency, HF: High Heart Frequency During Prolonged ECG.

The authors of the 5 reviews (4, 6, 9-11) listed in **Table 1**, studied 232 RCTs, all consistently reporting a positive effect of music therapy on the basic vital functions of infants. These reviews indicate improvements in HR, RR, oxygen saturation, feeding, and length of hospital stay in the preterm infants.

In the systemic review made by Mohan A. *et al*. (6), 13 RCT studies evaluating the analgesic effects of music are reported; however, these are not directly relevant to our survey.

Some reviews also document additional benefits of music therapy, including pain relief during medical procedures and reduction in parental stress. Review 11, a Cochrane review, included 25 trials recruiting 1532 infants and 691 parents. Within the trials, the music intervention varied widely in type, delivery, frequency, and duration. Music and voice were mainly characterized by calm, soft musical parameters in lullaby style, often integrating the song with mother's voice live or recorded. This review shows stable parameters in 1,532 preterm infants concerning RR and oxygen saturation, with a significant reduction in HR observed during and after each music session.

DISCUSSION

Our review demonstrates that music therapy seems to acquire the characteristics of a therapeutic practice to be used even in hospital settings for selected patients, such as preterm infants.

The studies we evaluated show increasing interest in this type of therapy, but they also demonstrate that patients are difficult to select in a homogeneous way, and numerous publications present biases that make them difficult to compare with others, involving patients with the same type of clinical condition. This makes it challenging to conduct meta-analyses in systematic literature reviews. Another aspect that significantly reduces the possibility of conducting research on large numbers of subjects is the lack of funding from pharmaceutical companies, which are not interested in this type of therapeutic procedure (26). However, with our review, we have highlighted that even though RCTs often involve small numbers of patients

and thus carry reduced scientific weight, systematic literature reviews which gather data from thousands of patients are able to demonstrate the scientific value of this therapy, which should therefore be encouraged and expanded. There are already some therapeutic protocols studied and published in literature, waiting only for adequate funding to be applied in pediatric hospital settings (27).

In the studies we analyzed, the music therapist was rarely involved in the study. The involvement of a music therapist is advisable to assess the choice of music and its method of delivery. In fact, music therapy is characterized by personally tailored music interventions initiated by a trained and qualified music therapist, which distinguishes music therapy from other music interventions, such as 'music medicine'.

Possible effect of music therapy on the nervous system of preterm infants

Neurophysiological research has also given a significant boost to music therapy by studying the neurological connections between various subcortical and cortical neuron nuclei that are stimulated through music, even in preterm infants.

Recent experimental studies have demonstrated how the auditory stimulus is transmitted from the outer hair cells and inner hair cells of the cochlea to the axons of the acoustic nerve, which convey the neural stimulus to the cochlear nuclei, both dorsal and ventral, at the level of the medulla oblongata. Other axons originating from the bulbar olivocochlear nuclei collect the auditory stimulus from the same cochlear cells. The MOC fibers (bundles of the medial olivocochlear system) carry electrical stimuli predominantly to the contralateral but also to the ipsilateral nuclei of the olivocochlear system, while the LOC fibers (bundles of the lateral olivocochlear system) carry them only to the ipsilateral nuclei of the same system, which is located below the fourth cerebral ventricle. The olivocochlear system sends and receives inputs (ascending through the brainstem, diencephalon, and brain) from neuronal axons of the lateral lemniscus nuclei and inferior colliculi, from the thalamic geniculate nuclei, from the auditory cortical center in the temporal lobe, from the prefrontal area, from the motor and sensory areas, from the visual area, and from the cerebellum. All these nerve cell nuclei present in various subcortical and cortical areas participate in the reception of the musical stimulus, as well as its tactile, sensory, visual, and motor processing (28).

At the level of the bilateral olivocortical nuclei in the brainstem, there are axons that send auditory-derived inputs to other cellular nuclei that control blood pH, form the respiratory center, and regulate the vasomotor center, which governs heart rate, vascular tone, blood pressure, and the systolic ejection force of the myocardium (28). Moreover, axons present in the inferior colliculus and thalamus release neurotransmitters that amplify or reduce axonal inputs, which also enter the bloodstream.

These complex nervous interactions, involving different areas of the central nervous system, may therefore explain the various functions that musical vibrations can have on preterm infants.

Role of neurotransmitters

One of the various pathogenetic mechanisms invoked to explain the beneficial effects of music therapy in neonates is the interaction of neurotransmitters, specifically the interaction between oxytocin and dopamine, and between oxytocin and cortisol (29). It is believed that music increases dopamine levels in the brain, which positively affects cognitive, psychological, and motor functions. Dopamine is produced by neurons in the basal nuclei that interact with neurons in the prefrontal cortex and other basal nuclei through four pathways of stimulus transmission: the 'meso-limbic pathway', the 'nigro-striatal pathway', the 'meso-cortical pathway' and the 'tubero-infundibular pathway'. The neurological stimulus induced by music particularly follows the 'meso-cortical pathway' of dopamine, which connects the 'ventral tegmental area' of the midbrain to the prefrontal cortex. This pathway is also activated in the regulation of emotions and feelings (30).

In these same areas, an interaction between cells that produce dopamine and those that produce oxytocin has been demonstrated, which together influence various social behaviors in humans, including sexual stimuli, mating behaviors, and mood swings. Some researchers define these neurological circuits as 'Circuits regulating pleasure and happiness' (31). On the other hand, music can significantly increase oxytocin levels and reduce salivary cortisol, as demonstrated by measuring salivary oxytocin concentrations in a group of subjects after lis-

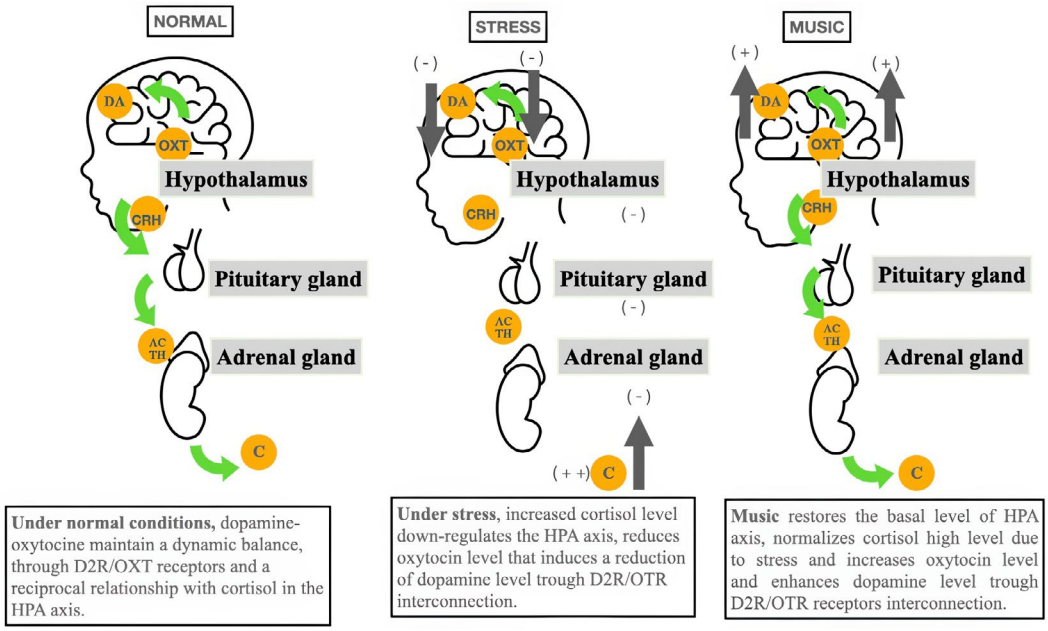

***Figure 2**. Music therapy and the hypothalamic-pituitary-adrenal (HPA) axis. Modified from: Dewan MV, et al. (25).*

DA: Dopamine; OXT: Oxytocin; HPA: Hypothalamus-Pituitary Gland-Adrenal Gland Axis; C: Cortisol; CHD: Corticotropin-Realising Hormon; ACTH: Adrenocorticotropic.

tening to slow-tempo relaxing music and fast-tempo exciting music (32). Other studies have shown a correlation between oxytocin production and a reduction in cortisol levels in subjects stimulated by music. When a subject is under stress, cortisol levels increase, which has a negative feedback mechanism on the hypothalamic-pituitary-adrenal axis, leading to a decrease in oxytocin levels. This would result in a down-regulation of dopamine through the interaction of D2R/OTR receptors (33, 34). However, musical stimulation reduces stress, normalizes cortisol levels, restores the dynamic balance of the hypothalamic-pituitary-adrenal axis, up-regulates oxytocin, and consequently increases dopamine levels through the interaction of D2R-OTR receptors (34-36) (**Figure 2**). Therefore, it is hypothesized that in children, music stimulates the nerve cells that produce these neurotransmitters, which are part of the happiness and pleasure circuit, affecting both the basal nuclei and various cortical areas, including the frontal cortical area. From here, pyramidal and extrapyramidal fibers originate, which can influence not only mood and social interactions but also the respiratory centers, heart rate, and the striated and smooth musculature of various organs and systems of the human body.

CONCLUSIONS

Neural and humoral interactions can explain the reduction in respiratory rate, heart rate, and the increase in oxygen saturation observed in preterm neonates during and after music therapy sessions, as an effect of the relaxing properties of music. In the studies we analyzed, lullaby music has so far proven to be the most commonly used. Also, this kind of music is not a drug, but it can induce the production of mediators similarly to a drug and can be used to properly maintain the vital functions in pre-term infants for its antistress effect. Recently it has been demonstrated also in subjects over 18 years of age that music therapy has an overall medium-to-large effect on stress-related outcomes (37). The numerous potential benefits and the absence of known side effects reported in newborns, suitable for this therapy and clinically stable, are a strong argument in favor of its use in NICU and Grow Care Units.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Authors have declared no conflict of interests.

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Authors' contributions

FB and AB wrote the manuscript.

Ethical approval

Human studies and subjects

N/A.

Data sharing and data accessibility

Data are available upon motivated request to the Corresponding Author.

Publication ethics

Plagiarism

Authors declare no potentially overlapping publications with the content of this manuscript and all original studies are cited as appropriate.

Data falsification and fabrication

All the data corresponds to the real.

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