Effects of Music Therapy on Preterm Neonates and Their Parents

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GRADUATION THESIS

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Thesis mentor: Associate Professor Iva Bilić Čače, MD, PhD

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The graduation thesis contains 31 pages, 1 figure, 0 tables, 116 references.

Preface

Becoming a pediatrician was the driving force behind my decision to enroll into medical school. It was therefore a natural choice for me to dive into this area for my final thesis.

First and foremost, I am deeply grateful to my family and my friends for their support and encouragement throughout my academic journey. They have been a big source of motivation. A heartfelt shoutout goes to my son, who added his own creative flair to the manuscript by sprinkling in random letters whenever I did not pay attention.

I would furthermore like to express gratitude towards my mentor, whose guidance and expertise have been invaluable. Your ideas and comments helped me to acquire a deeper understanding of the subject. I am also grateful for my English teacher for her feedback on language, which helped me to refine my writing and communicate my ideas effectively.

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List of abbreviations and acronyms

AI	artificial intelligence
ANS	autonomic nervous system
CGA	corrected gestational age
CMT	creative music therapy
CNS	central nervous system
EPDS	Edinburgh Postnatal Depression Scale
GA	gestational age
GW	gestational week
HADS	Hospital Anxiety and Depression Rating Scale
HPA	hypothalamic-pituitary-adrenal
HR	heart rate
HRV	heart rate variability
IV	intravenous
KBC	Clinical Hospital Center (Cro. Klinički bolnički centar)
LongSTEP	Longitudinal Study of Music Therapy's Effectiveness for Premature Infants and Their Caregivers
MRI	magnetic resonance imaging
MT	music therapy
NICU	Neonatal intensive care unit
NNBAS	Brazelton's Neonatal Neuro Behavioural Assessment Scale
PAL	Pacifier-activated-lullaby system
PBQ	Postpartum Bonding Questionnaire
PIOMI	premature infant oral motor intervention
PIPP	Premature Infant Pain Profile
PIPP-R	Premature Infant Pain Profile Revised
POFRAS	Preterm Oral Feeding Readiness Scale
PPROM	Preterm Premature Rupture of the Membranes
RCT	randomized controlled trial
RDS	Respiratory Distress Syndrome
REM	rapid eye movement
SENSE	Supporting and Enhancing NICU Sensory Experiences
SGA	small for gestational age

STAI	State-Trait Anxiety Inventory
WFMT	World Federation of Music Therapy
WHO	World Health Organization

1 Introduction

1.1 Defining Music Therapy

Music is an inherent part of human existence. It can be heard on the radio during the commute to work as well as in shops and cafes. Lullabies gently accompany children to sleep at bedtime. In fact, it is such a prevalent component of our daily activities that certain songs or melodies are strongly associated with specific emotions (1). Early encounters with music often come from songs sung by parents during infancy or even earlier, in the prenatal period (2). Caregiver-infant musical interactions are observed across various human cultures (3).

Beyond its emotional impact, music also exerts physiological effects, such as inducing brain plasticity, making it a valuable tool for healthcare applications (4). While simply playing pre-recorded music for patients taps into some of these effects, live music therapy (MT) is a more systematic approach (5). According to the World Federation of Music Therapy (WFMT), music therapy is the incorporation of music into health care, schools, or everyday life with the purpose to improve the quality of life and well-being of individual people, as well as groups or communities. It follows a holistic concept, based on professional guidelines adjusted to cultural, social, and political backgrounds, which aims at improving social, physical, cognitive-emotional, and spiritual enhancement (6).

1.2 Music Therapy in Premature Infants

1.2.1 Prematurity and Its Impact

Preterm infants are infants born before the age of 37 gestational weeks (GW) (duration of pregnancy, starting with the first day of the last period). Based on their exact gestational age (GA), they can be further subdivided into late preterm from 32 to 37 GW, very preterm from 28 to 32 GW, and extremely preterm for infants born before 28 GW (7).

In 2020, 9.9% of babies born worldwide were born prematurely (8). There are, however, large disparities on the regional, but also national levels. Serbia and Moldova have the lowest rates of preterm births with 3.8 and 4%, respectively. Approximately two-thirds of all preterm births occurred in southern Asia and sub-Saharan Africa, where the prevalence rates were over 13%. In the United States of America, 10% of live births are preterm births, while the prevalence rates in Europe range from 5.4 to 12.0% (9,10).

One third of preterm deliveries are the consequence of induction of labor or cesarean section due to fetal indications, such as intrauterine growth restriction or maternal indications, such as

eclampsia (11). The rest of preterm deliveries are spontaneous, either due to spontaneous preterm labor or preterm premature rupture of the membranes (PPROM). The latter two could be caused by multiple mechanisms, such as inflammation, uteroplacental ischemia, stress, or uterine overdistension (11).

Prematurity is the leading cause of death for children below the age of five. Apart from a higher mortality rate in this group of newborns compared to those born at term, infants born prematurely often face serious medical complications, such as infections, respiratory distress syndrome (RDS), necrotizing enterocolitis, or intraventricular hemorrhage. Additionally, there are many long-term consequences, such as impaired development, disability, and chronic diseases in the adult age (7,10,12). Due to medical progress the overall survival of premature infants is high today, which shifts the focus of care towards enhancing the neurodevelopmental outcome for these infants (13).

There is an inverse correlation between the infants' GA and their estimated stay in the hospital, with a study at the Princess Royal Maternity Hospital in Glasgow reporting an average stay of 101 days for babies born in GW 25, compared to 17 days for children born at 33 weeks (14). Hospitalization exposes the infant to various stressors, including noise, bright light, painful medical procedures, as well as decreased maternal contact (15,16).

The resulting stress can modulate the hypothalamic-pituitary-adrenal axis (HPA), affecting a child's health across their entire life (17). Continuous noise exposure, for example, does not only have acute effects on the physiological responses of the newborn; it also places the infant at risk for abnormal sensory development, hearing loss, and language difficulties (18,19). Given the important developmental changes happening during these early days, preterm neonates are highly vulnerable to negative external influences, such as noise or pain, which can hinder proper development. However, there is at the same time high receptivity for potentially beneficial sensory influences (20).

1.2.2 Application of Music Therapy in Premature Newborns

MT finds application across various fields of pediatrics, for example, in oncology, neurology, and psychiatry, and, notably, neonatology (5). MT in premature infants became the interest of research in the 1970s, and since the 1990s, its application has been steadily growing (21). In 2017, twenty-eight neonatology wards in German-speaking countries used MT (22).

Fetal reactivity to sound is already present in utero (3,23–25). At birth, term infants possess all the neural foundations required to process musical elements. Premature infants show cortical

activity in response to sound from the GA of 33 weeks (26,27). Lullaby music, even if unfamiliar, has been shown to induce relaxation in infants, indicating that there might be some predisposition in infants to respond to music (28). In the neonatal intensive care unit (NICU), MT sessions are adjusted to the environmental sounds to mask ambient noise and make the environment more comfortable for the infant. Furthermore, targeted interventions are used to achieve physiological as well as interpersonal improvement (29,30).

There is a variety of different MT interventions for infants and their families available today, which can be assigned to three main groups: receptive, improvizational and recreative MT. The basis for these interventions lies in different theoretical concepts, ranging from behavioral theories and developmental psychology to trauma and attachment-oriented approaches (21).

1.2.2.1 Receptive Music Therapy

Receptive MT methods are those, in which the infant listens to either recorded or live music (31). They were mainly used in the past, while today, a more active, improvising approach is undertaken.

Environmental Music Therapy is a general approach aimed at creating a calm and secure environment by masking ambient noise in the NICU setting, while Individually Provided Sustained Music helps the infant to relax, and aims to reduce stress-related behaviors (21).

Breathing and singing entrainments are indicated in infants >32 GW with a high amount of distress or irritability, such as inconsolable crying or even with the Neonatal Withdrawal Syndrome (21). Breathing entrainment uses specific instruments, melodies, or maternal voice that mimic uterine sounds, while in the second intervention, a therapist tries to connect to the infant with their voice, tailoring their singing to the physiological and motor reactions of the child (21).

Music and Multimodal Stimulation, a combination of humming or singing with tactile, vestibular, and visual stimulation, is used to stimulate the neurologic development of premature newborns while slowly increasing their capacity to tolerate stimulation and to create homeostasis (21).

Music Reinforced Non-Nutritive Sucking is an intervention that is based on behavioral therapy and is indicated for clinically-stable preterm infants that have trouble with feeding or need help transitioning from tube to bottle feeding (21). Pacifier-activated devices are used to enhance non-nutritive sucking behaviors in premature infants. The pacifier-activated-lullaby system (PAL), for example, consists of a sensor, a pacifier, and a receiver. Pressure thresholds can be

set individually. If the infant is sucking effectively, an auditory stimulus is delivered. Maternal singing is a positive stimulus frequently used for this purpose (32).

1.2.2.2 Improvisational Music Therapy

Improvisational MT interventions are based on observing the infant's behavior and then tailoring and constantly modifying melodies based on the infant's respiration, gestures, and facial expressions (33). The two main approaches are Multi-sensory Stimulation and Creative Music Therapy (CMT).

Multi-sensory Stimulation is used to enhance the development of premature infants and to stabilize the child. This intervention is similar to Music and Multimodal Stimulation, which was mentioned before. The main difference between the two interventions is that the therapist uses improvization to create individualized melodies, tailored to the current cues in the infant, instead of singing or humming a fixed melody. The intervention can be used for young and fragile premature children >28 GW (21).

Taking the previous concepts one step further, CMT does not only regard the needs and resources of the premature infant, but also allows for the incorporation of their family, for example, in terms of active participation by singing, or just by listening, thereby improving bonding (21,34). Based on the infant's breathing pattern, mimics, and gestures, a therapist creates an individual response by humming in a lullaby style, regulating the pitch and rate according on the infant's current state. Touch can be incorporated if tolerated by the infant (35).

1.2.2.3 Recreative Music Therapy

Recreative MT interventions aim to strengthen the resources and facilitate maternal-infant bonding. Auditory Stimulation with the Mother's Voice creates a sense of familiarity by playing recordings of the mother's voice while she is absent. This does not only calm the child down and facilitate bonding, but also helps the mother to process the traumatic situation and strengthen her identity as a parent. This intervention can be used independently of GA and could be implicated during pregnancy if preterm delivery is expected (21).

Finally, Song of Kin for Caregiver Support, a concept used by Loewy, incorporates cultural and religious aspects by working with songs that are familiar or in some way meaningful to the

infant‘s family (36). The HeartSong intervention combines a parent-selected Song of Kin with the infant’s recorded heartbeat to support bereavement and bonding (37).

2 Aims and Objectives

MT has proven to be an effective complementary treatment across many fields. To the best of our knowledge, it is not yet implemented in Croatian NICUs. The aim of this literature review is to, ultimately, improve the quality of care for premature infants and their families by providing a comprehensive overview of the effects of MT and, additionally, evaluating the feasibility and possible strategies for implementing MT programs for infants in the Clinical Hospital Center (KBC) Rijeka.

Objectives:

1. To review existing literature on the effects of MT interventions in the NICU, focusing not only on premature infants but also their families.
2. To identify common challenges arising in the NICU setting and explore how MT could contribute to addressing them effectively, thereby improving the overall well-being of premature infants and their families.
3. To determine physiological, developmental, and psychological benefits associated with MT interventions in the NICU.
4. To investigate the influence of MT on parental mental health as well as parent-infant dynamics in the NICU.
5. To assess the perceptions, attitudes, and potential concerns of parents and health care professionals regarding MT and to gain a better understanding of the acceptance and feasibility of such programs.
6. To determine prerequisites, guidelines, and necessary resources for the successful implementation of MT within the NICU of the KBC Rijeka.

3 Literature Review

3.1 Effects of Music Therapy on the Infant

3.1.1 Physiological Parameters

Monitoring in the NICU creates an environment full of noise. This auditory stimulation, if excessive, can result in negative physiological responses, which can be quantified by

physiological parameters that indicate stress in premature infants, such as apneas and variations in heart rate (HR), blood pressure instability, and hypoxemia (19,24,38–41).
Music masks ambient noise, thus reducing stress and improving physiological stability (29). The heart rate of a stable preterm infant should be between 120 and 160 beats/min, and they should breathe regularly, at a rate of 30 to 60 breaths per minute, with an oxygen saturation of 92 to 96% (42).

3.1.1.1 Heart Rate

Multiple studies have investigated the effects of various music interventions on the HR of premature infants. Table 1 provides an overview of different methods and outcomes found in different clinical trials (40–47). Premature infants showed lower HR during lullaby interventions and interventions using the Gato box, an instrument that is used to mimic the heartbeat a fetus would hear in the womb, while interventions with the Ocean disc led to a lower HR after the session (43). Live music therapy can lead to a lower HR, regardless of the state of wakefulness (40,44,47,48).
Notably, results of trials using recorded music are mixed. Infants exposed to relaxing music generated by artificial intelligence (AI) had a lower HR than the control group (45). Recorded lullabies led to a lower HR during and after the intervention, in comparison to recorded music by Mozart, which led to a decreased HR during the session only (42). Other trials, however, failed to achieve any significant results on the HR by using recorded lullabies or live MT (41,46).
A potential explanation for the benefits of music observed in the majority of the trials is its effect on the autonomic nervous system (ANS). In a basal state, the parasympathetic nervous system dominates the regulation of HR. In premature infants, however, the sympathetic nervous system is dominant, leading to a higher HR. Music establishes a balance between both entities of the autonomic nervous system. This effect is then reflected by a decrease in HR and the stabilization of the respiratory rate (45).
The degree of ANS maturation can be assessed by measuring the heart rate variability (HRV), which refers to the fluctuation of beat-to-beat intervals as a result of the continuous counteracting input from the sympathetic and parasympathetic nervous system on the heart (49). Assessing HRV can be a useful tool to determine physiological maturation. As parasympathetic activity increases, so does HRV (50). Pentatonic live music did not have a

significant effect on the HR in a clinical trial conducted by Ranger et al, but the authors did find significant changes in HRV, supporting the aforementioned explanation (51).

3.1.1.2 Respiratory Rate and Oxygen Saturation

Music generated by artificial intelligence lowered the respiratory rate in a small randomized controlled trial (RCT) consisting of 17 premature infants in Spain, which the authors attributed to the stabilization of the autonomic nervous system (45). Kobus and colleagues investigated whether MT applied during sleep or wakefulness yields different effects regarding the infant's vital parameters. An improvement in respiratory rates and oxygen saturation were found after each live session, regardless of the state of wakefulness. During the intervention, higher oxygen saturation and a lower respiratory rate were observed if the infants received therapy during sleep (44).

The Ocean disc, an instrument that imitates fluid sounds of the womb, can be used to mirror and manipulate the infant's respiratory pattern. It was able to significantly improve the oxygen saturation in a RCT by Loewy and colleagues, while a trend towards higher respiratory rates was observed (43).

Menke and colleagues conducted a pilot study in 2021, investigating the influence of interactive MT on parental stress and the physiological development of 65 premature infants. Among their main findings was a significant reduction in the length of caffeine therapy, which they linked to the ability of music to stabilize breathing patterns, thereby reducing phases of apnea (33).

According to different studies, the effect of recorded music on oxygen saturation, heart, and respiratory rate varies (41,42,46). A non-controlled study exposing 12 preterm infants to classical music showed inconsistent effects on the oxygen saturation (19). Furthermore, no effect on oxygen saturation and respiratory rate was noted in some trials involving live music (47,51).

3.1.2 Sleep and Relaxation

Being exposed to noise can alter a premature infant's behavior. Stress can elicit certain changes that can, in turn, serve as cues for clinicians to evaluate the infant's current state. An infant in distress may, besides the aforementioned physiologic alterations, be irritable, hyperalert, and cries a lot. Additionally, stressed infants sleep less (24). Observing the motor system can further point towards stress; stretching or arching of the trunk, with extended arms and legs, finger

moving and grimacing can be displayed. Further signs include hiccupping, frequent sneezing, and yawning (24).

An observational study found facial alterations indicating stress and changes in sleep and wakefulness patterns among premature infants subjected to noise; further reactions to noise included an increase in blink and startle reflexes (52). Rapid eye movement (REM) sleep is important for weight gain and maturation of premature infants. Disturbing sounds may alter the sleep-wake cycles, thereby disrupting or preventing REM phases, which are important for processes, such as maturation and weight gain (41).

Music has the potential to decrease sleep interruptions and promote the maturation of sleep patterns among premature infants (27,53). Recorded lullabies have increased the duration of sleep in a clinical trial study involving 90 premature infants (46). Loewy and colleagues investigated the effects of live MT on premature infants suffering from RDS, sepsis, or being short for gestational age (SGA). They observed, that MT interventions using the ocean disc improved the premature infants' sleeping patterns and put them in a more quiet state (43).

Arnon and colleagues compared the effects of recorded and live music therapy on stable infants' behavior. Live MT had a soothing effect on the infants, while recorded music showed no changes on stable infants' behavior (47).

Besides affecting sleep, music can also comfort infants. Keith and colleagues found a significant reduction in the frequency as well as duration of episodes of inconsolable crying among infants listening to music (18). Similarly, lullabies written and sung by the mother also reduced crying (54).

3.1.3 Feeding and Weight Gain

Due to a lack of physical and cognitive development, premature infants often have difficulties with oral intake, mainly due to being unable to properly coordinate sucking, swallowing, and breathing (55). This is often accompanied by failure to gain weight (56).

Most infants born before 32 GW need to be tube-fed. The point of transitioning to proper feeding is determined by assessing whether the infant displays signs of readiness, such as non-nutritive sucking or rooting. Sucking behaviors must be encouraged, as they can facilitate the maturation of oral feeding behavior (57).

Several studies have looked into the effectiveness of pacifier-activated devices, which aim to increase sucking behaviors by music reinforcement. Standley and colleagues found PAL to increase nipple feeding rates in premature infants (58). A randomized trial at the Vanderbilt

University Medical Center NICU implemented the PAL before the infant's feeding time. After five days of therapy, a significant improvement was noted in the oral feeding rate, volume of oral intake, and the number of oral feedings per day as compared to the control group. Furthermore, full oral feeds were achieved one week earlier in the experimental group. The infants' weight at discharge, however, was without any improvement as compared to the control group. (32).

In the pilot study conducted by Menke and colleagues, a significantly shorter duration of nasogastric or orogastric tube feeding was found among the premature infants in the experimental group. The authors assumed that these findings resulted from MT facilitating the establishment of a suck-swallow-breath rhythm. These improvements, in turn, increased weight gain and facilitated a quicker discharge: the experimental group's stay in the hospital was on average two weeks shorter (33). Similarly, Loewy et al. found parent-preferred lullabies to improve feeding behaviors and sucking patterns (43).

Music can be used as an additional measure to enhance the clinical effects of other interventions, such as the Premature Infant Oral Motor Intervention (PIOMI), a protocol specifically designed to improve feeding skills in premature infants. Shokri and colleagues recently conducted research on the effects of PIOMI alone versus in combination with music by Mozart in 52 premature infants (55). Infants in the experimental group scored significantly higher on the Preterm Oral Feeding Readiness Scale (POFRAS), achieved oral feedings earlier, and drank more milk than the infants in the control group. On average, these infants were discharged earlier, an observation that was not statistically significant but still has clinical relevance since it reduces the burden on the infants and their families, while at the same time keeping the cost lower. Despite all these improvements, the weight gain between those two groups did not differ significantly (55).

3.1.4 Neurodevelopment

Preterm birth is a risk factor for the development of neurobehavioral and cognitive problems that persist during childhood and even into adulthood. Specifically, challenges often arise in the field of motor, cognitive, and sensory development (13,59). Long-term results include movement disorders, problems with executive functioning, working memory, and behavior. Impaired hearing and vision can lead to problems with language formation and processing as well as academic challenges (13). All these problems can be linked to various factors arising from preterm birth itself as well as hospitalization.

Premature infants are in a particularly vulnerable phase as they undergo fast developmental changes in their neural development and, especially, the auditory system. In the womb, they would have been exposed to the rhythmic maternal heartbeat as well as the mother's voice (23,25). During hospitalization, on one hand, infants experience auditory as well as socio-emotional isolation, which results in a lack of sensory experiences. On the other hand, premature infants are constantly exposed to stressors, such as noise, light, and painful procedures (59–61). Stress exposure manifests itself with a loss of excitatory synapses in the hippocampal and prefrontal cortical areas, as well as alterations in the amygdala and even death of neurons (23). Neonates who were kept in private, and relatively quiet, rooms, showed deficits in brain maturation, especially in regards to language development, but there was also a trend towards motor deficits (23).

Monson and colleagues compared the language and auditory exposure of fetuses versus preterm infants. While preterm infants had a greater daily exposure to noise and electronic sounds, they also had a lower daily exposure to language than fetuses. For some infants, this exposure added up to a deficit of 150 hours for the entire preterm period (62). In a survey from 2021, nurses reported that they mostly speak to infants close to term GA yet whisper or remain completely silent with infants born at GW 28 or less (63).

Auditory stimulation, for example, in the form of music is important to enhance the central auditory processing, which, in turn, is the foundation for the future development of language (64). Brain development is highly dependent on early auditory experiences, as good quality auditory experiences, such as music, can facilitate neuronal differentiation and enhance the production of nerve growth factor. Furthermore, synaptic plasticity and neuronal learning are modulated and facilitated by music (23).

Haslbeck and colleagues assessed the short and medium-term effects of CMT on the brain with magnetic resonance imaging (MRI) in a pilot study. They found higher connectivity of functional brain networks, especially in areas associated with higher-order cognitive, socio-emotional, and motor functions, such as thalamocortical, prefrontal, supplementary motor, and temporal regions; these functional changes came without any structural changes to the brain. However, the dropout rate among the control group was relatively high, which led to a small overall sample size of 40 infants. A further shortcoming of this study is the lack of information about the long-term effects (59). Similarly, a MRI imaging study assessing the effects of early music interventions in very premature infants found evidence for enhanced axonal growth and oligodendroglial differentiation as well as an enhanced maturation of cortical grey matter regions involved in auditory, socio-emotional, and cognitive processing (65).

Additionally, mother's involvement is essential for neuronal development and providing positive sensory experiences by auditory stimulation, since an early and nurturing maternal-infant relationship effectively reduces stress and improves the long-term neurodevelopmental outcome (23). Anusha and Radhika exposed premature infants to an auditory stimulation program consisting of a guided talk by the mother before feeding and additionally stimulated the child with music by a rattle twice a day. After one week, the experimental group performed significantly better on the Brazelton's Neonatal Neuro Behavioural Assessment Scale (NNBAS), which indicates a positive influence of auditory interventions on the infants' neurobehavior (61).

Moreover, stimulation with the maternal voice has been shown to also have beneficial effects on the premature infant's development through the first six postnatal years: 24 preterm infants were exposed to recordings of the maternal voice while being in the NICU. A series of developmental tests were performed at the age of five, 20, 56 months, and six years. Stimulated infants scored higher on the Griffiths Developmental Quotient at the age of five months. Furthermore, they started to use two-word sentences at the age of 17 months, while the control group started at 20 months, and showed a better understanding of speech at the age of six (66). The authors concluded that auditory stimulation may support the central nervous system (CNS) in developing neurobehavioral functions. However, the infants in the intervention group were also more often breastfed and their mothers reported feeling less overwhelmed. These two factors, according to the authors, may have contributed to the aforementioned results, since human milk does play a role in neurodevelopment. They stated that the mother's voice, a "sensory bridge into postnatal life," could also be crucial in initiating important developmental events that, eventually, lead to language acquisition (66).

Different programs aiming at sensory stimulation include music. The Supporting and Enhancing NICU Sensory Experiences (SENSE) program includes multiple sensory stimulations, such as tactile, auditory, visual, olfactory, and vestibular, which are individually adjusted based on the level of immaturity of the infant. Results of a pilot study showed improved neurobehavior at the time of discharge from the NICU, with the infants displaying less asymmetry. By providing the parents with the conditions for active participation, the program simultaneously empowers the parents and helps them with coping (67). Detmer and colleagues conducted a pilot study investigating the long-term developmental effects of Multimodal Neurologic Enhancement. Children who had participated in the program during their stay in the NICU performed significantly better in the visual reception and the early learning composite domains of the Mullen Scales of Early Learning (68).

3.1.5 Pain Management

In the first two weeks of staying in the NICU, a premature infant undergoes an average of 134 painful procedures, such as endotracheal suctioning and blood sampling. These interventions do not only lead to acute discomfort and physiological disturbances, such as bradycardia or hypertension. Moreover, experiencing pain in early life influences neurological development, impacting the future stress response and causing molecular as well as epigenetic changes (69,70).

Analgesia is therefore a crucial concern when dealing with premature infants. Pharmacological options for pain management are topical and local agents, as well as systemic analgesics, such as paracetamol and opioids (71). Breastfeeding, skin-to-skin contact, and sweet-tasting solutions are non-pharmacological measures that offer a distraction from the painful stimulus (70). Their effectiveness, however, is inconsistent among children (72).

Current recommendations favor a multimodal approach, combining non-pharmacological options with medication. In some instances, using several non-pharmacologic measures in combination and thereby increasing their effect is recommended to reduce or avoid the use of pharmacologic agents and the associated risks (71). For brief, mild pain, such as during heel prick procedures, a combination of oral sucrose and skin-to-skin contact is usually sufficient to alleviate the pain. For lumbar puncture and similar procedures, topical analgesia is the method of choice. For more complicated procedures, such as placing a central venous catheter, additional measures include Acetaminophen and, if necessary, a short-acting opioid agent (71).

Several studies have looked into whether music, either alone or in combination with other measures, would be a useful tool for pain relief in neonates. Shah and colleagues investigated pain perception according to the Premature Infant Pain Profile - Revised (PIPP-R) scale during a heel prick procedure. In a crossover trial, 35 neonates with a mean GA of 35 weeks received either oral sucrose, music, or a combination of both; their PIPP-R scores were lower when both modalities were combined. If used as a stand-alone measure, both measures were equally effective in reducing pain (73). This indicates that music can be a synergistic adjunct to other, well-established strategies. While some trials relying on classical music composed by Mozart, lullabies or music that the mother listened to during pregnancy supported the aforementioned results, other trials failed to achieve the same results during heel prick procedures (74–77).

An RCT in Tehran assessed the effectiveness of lullaby music on pain severity during and after venipuncture. One hundred and twenty preterm neonates were assigned to either sucrose,

lullaby music, the combination of both, and a control group. During the procedure, as well as after 30 seconds and 10 minutes, their pain was assessed using the Premature Infant Pain Profile (PIPP) scale. Lullaby music in combination with sucrose was able to relieve pain during and immediately after the procedure, while it only lowered the pain 30 seconds after the venipuncture when used as a stand-alone measure (78).

Another RCT compared the effectiveness of oral glucose and/or listening to lullabies during oronasopharyngeal suctioning and tracheal tube procedures, showing significantly lower pain in the intervention groups (79).

Qiu and colleagues explored the potential of CMT in relieving pain for premature infants undergoing various other painful procedures, such as nasal aspiration, adhesive removal, and intravenous (IV) cannulation. The experimental group exhibited a significant decrease in the PIPP score after two weeks, while an increase was observed in the control group. There was no statistically significant effect on the cortisol concentrations, which can be used to measure stress in children. However, the beta-endorphin concentration was significantly increased among the experimental group, which may be responsible for a decreased pain response (72,80).

3.1.6 Adverse Effects

Available data on safety are rather scarce (81). Except for the physiological instability among premature infants with severe brain injury, no adverse effects have been reported, when using recorded lullabies or Mozart music, as well as live music and voice (42,48,82,83).

3.2 Effects on the Parents

3.2.1 Parental Mental Health and Bonding

Having a premature infant is a stressful experience for parents. Preterm labor often occurs unexpectedly, catching parents off guard before they are mentally prepared to become parents (84). In the NICU, they frequently encounter challenges, such as the feeling of a lack of control, being emotionally and physically separated from their child, and insufficient communication and emotional support (85). Carter and colleagues noted a higher rate of anxiety and depression assessed with the hospital anxiety and depression rating scale (HADS), among parents of premature infants admitted to the NICU (86). Additionally, the symptoms of Acute Stress Disorder as well as the Post-traumatic Stress Disorder may manifest in some individuals (84).

Separation not only intensifies the aforementioned symptoms in parents but also affects the parent-infant relationship (87,88). Emotional connections and a healthy relationship with parents are crucial for an infant's development. Two distinctive processes involved in the formation of relationships are attachment and bonding, both of which take place during the pregnancy as well as the early postnatal life. Attachment refers to how the child builds a relationship with its caregiver, while bonding pertains to the feelings, thoughts, and behavior of parents towards their child. Preterm birth and hospitalization of the infant can disrupt these processes (84).

Being separated from their parents affects neurodevelopment and bonding, which ultimately alters emotional programming and impacts the infants' future stress response. Maternal closeness has been proven to decrease cortisol levels and pain responses in premature newborns and enhance their neurological development (23,88).

Today, family-centered care is the standard approach in neonatology (23,24,89). Various strategies in the NICU aim to facilitate closeness and alleviate parental stress, that is, the use of private rooms, creating a soothing atmosphere and providing chairs or beds for parents to be with their newborn as well as measures to increase parental visiting hours and educating and including parents into care (88).

MT can be a useful tool enabling parents to actively participate and connect to their infant. Kobus and colleagues found that MT reduces symptoms of depression and maternal stress while enhancing maternal competencies to interact with the child, thereby facilitating parent-infant bonding (90). Similarly, Kehl and colleagues conducted a mixed-method pilot study on 16 parent couples and their premature infants in Zurich (34). In the intervention group, they found a significant reduction in state anxiety assessed by the State-Trait Anxiety Inventory (STAI) and depressive symptoms assessed by the Edinburgh Postnatal Depression Scale (EPDS). Parental view was assessed using semi-structured interviews, which revealed that CMT created a sense of closeness and intimacy between the parents and their infants. They suggest that CMT serves as a coping strategy, supporting the infant-parent bonding process by alleviating symptoms of anxiety, depression, and stress (34).

Several studies support the aforementioned findings: Menke and colleagues conducted a randomized controlled pilot study with 65 parent-infant pairs that indicated that live-improvised interactive MT successfully reduces parental stress (33). Loewy and colleagues had similar results (43).

Combining live harp music with kangaroo care has been shown to reduce maternal anxiety in a prospective trial including 52 mother-infant pairs in Israel (91). Especially when introduced

early, MT decreases maternal anxiety levels, supposedly by offering an opportunity for active involvement and thereby enriching parents in their new role (92).

Two studies found that MT focused exclusively on the parents successfully reduces stress and anxiety levels (93,94). Notably, even when just applied to the child, recorded maternal singing benefits the mothers, as well, as indicated by Cevasco: mothers of premature children reported better coping due to the fact that their child was exposed to the mother's voice while in the NICU (95).

The multinational Longitudinal Study of Music Therapy's Effectiveness for Premature Infants and Their Caregivers (LongSTEP) explored the influence of MT on bonding, parents' well-being, and infant development during their first year of life, whereby the effects both during the NICU hospitalization and post-discharge were monitored. Despite generally being well-tolerated by parents, the study found no significant effect of MT on bonding based on the Postpartum Bonding Questionnaire (PBQ), parental mental health, or infant development (96).

3.2.2 Breastfeeding

The World Health Organization (WHO) recommends that children should be exclusively breastfed for the first six months and afterward continue to receive breast milk for up to two years of age or longer (97). Maternal milk protects infants against infections and reduces newborn mortality, while at the same time accelerating neurodevelopment (98,99). Therefore, premature infants should be breastfed as soon as possible if they are clinically stable (100). Implementing these recommendations in the NICU setting is not always easy and, often, infants receive either donor milk or formula instead. Possible interventions to improve feeding in premature infants were discussed earlier. This chapter focuses on maternal problems with breastfeeding.

Common challenges leading to problems with maternal milk supply are the infant's inability to breastfeed effectively, a delay in initiating breastfeeding, and irregular or infrequent emptying of the breast (101). The longer an infant's hospitalization, the more likely is the mother to discontinue lactation due to maternal stress, inconvenience of long-term milk expression, and insufficient encouragement as the major reasons. Especially breast pump-dependent mothers are at risk of encountering difficulties when initiating as well as maintaining lactation. Frequent consequences are milk volume insufficiency to meet the nutritional demands of the premature infant as well as obtaining low-fat, high-lactose milk which slows down weight gain (102).

Maternal psychological distress can impair lactation (102). As mentioned before, MT can reduce parental stress and anxiety, which could, in turn, facilitate breastfeeding. It was found that listening to flute-based MT while pumping reduces stress and results in a significantly higher volume of breast milk among mothers of premature infants in a small trial (103). However, a study conducted in Istanbul, where women listened to music before using the breast pump, failed to find a significant increase in breast milk volume, despite lowered stress levels (104).

In addition, music can affect lactation by increasing levels of oxytocin, the key hormone responsible for the let-down reflex, causing milk to be released during breastfeeding as a response to the infant's suckling or external stimuli, such as crying (105). Additionally, the release of prolactin is promoted, which, in turn, enhances milk production (106). A small clinical trial conducted by Sefid Haji and colleagues investigated the effects of listening to lullabies on the composition and volume of breast milk in mothers of premature infants. Volume of breast milk, fat content, albumin concentration, and total protein content increased in the group of mothers who were listening to music, which supports the thesis that MT may be beneficial for milk production (106). Similarly, Keith and colleagues found that mothers who listened to recorded music while pumping produced more milk with a higher fat content (107).

MT may not only be beneficial during the period of hospitalization, but also during the period following hospital discharge. Moreover, Vianna and colleaguesconducted an RCT in which mothers of premature neonates were exposed to an hour-long MT session three times weekly. Breastfeeding rates were measured at the time of hospital discharge, as well as a few days afterward and after one and two months (108). The intervention group displayed significantly higher breastfeeding rates when being discharged as well as during the first follow-up visit. A positive, but statistically not significant, trend in breastfeeding rates was also observed during the second and third follow-ups (108).

4 Discussion

Premature birth presents a significant challenge for the whole family. Premature infants are, on the one hand, faced with sensory deprivation due to not being in the uterine environment and, on the other hand, are exposed to noise and stressful situations. These factors do not only have an acute impact, but also long lasting consequences on the infants' neurodevelopment, especially in the cognitive and sensory domains, and their future stress response. Preterm birth

furthermore impacts the parents, causing stress and affecting their mental health as well as infant-parent bonding.

Live MT seems to have a beneficial effect on the heart rate, while the effects on other physiological parameters are inconclusive. During hospitalization, MT can be a useful adjunct in pain management, as it has been shown to effectively reduce procedural pain, particularly in combination with other non-pharmacological measures. Furthermore, MT interventions, such as PAL, are useful tools that facilitate an early transition from tube feeding and enhance the overall oral intake and thus may lead to an earlier hospital discharge for premature infants. At the same time, breastfeeding can be promoted due to the ability of music to enhance milk release, which enables the infant to receive all the benefits that breastmilk can offer. This is not only significant for the infants and their families, as it shortens the exposure to stress and separation, but also brings economic benefits through potential cost reductions associated with a shorter hospitalization. There is limited, but promising evidence about the short- as well as long-term effectiveness of MT on neural development and behavior, which indicates that the impact of these interventions extends far beyond the acute application during hospitalization.

Due to differences in study design, it is difficult to compare and generalize existing findings, especially since the interventions are very diverse, ranging from recorded music over maternal singing to multimodal stimulation. Moreover, the sample sizes were variable and often low and some pilot studies included in this literature review included very few infants. Although they might not offer a high level of evidence, they are still useful as they give a preview of what is yet to come in future clinical trials. Additionally, the intervals, lengths, and the overall duration of interventions were variable among different clinical trials and not all interventions were performed by a certified music therapist. Emery and colleagues however, demonstrated the efficacy of both intensive-intermittent and standard-spaced MT protocols, suggesting that the exact dosing might not have a pronounced impact on therapeutic outcomes (109).

Future research should be focused on providing specific MT interventions in a standardized manner, conducted by trained specialists to enhance comparability across clinical trials.

Although MT seems to be generally well-tolerated, therapists should be cautious in special, clinically less stable groups of infants (110). An RCT indicates physiological instability among preterm infants with severe brain injury during MT, which suggests that standard interventions might not be suitable for all infants (82). For instance, according to Haslbeck and Bassler, CMZ is only recommended in stable infants. This leaves room for further, detailed research to find more individualized approaches that are both efficient and safe in special groups of patients

(35). A preview into future research is provided in an ongoing trial in the Netherlands that is currently investigating the feasibility of delivering MT to extremely premature infants (111).
MT sessions have been shown to decrease parental stress and alleviate symptoms of anxiety and depression, while simultaneously strengthening, parental competencies and creating a sense of closeness to their child. There have been mixed results on the possible long-term effects of MT on these matters.
Parents in most studies perceived MT as positive and enriching, which indicates a high level of general satisfaction (54,95,110,112). MT is seen as a valuable refuge that enables them to relax and temporarily detach from the challenges they face. Furthermore, MT facilitated the interaction with their infants and supported their transition from the NICU environment to their homes (94,113).
According to a survey, nurses believed that the NICU environment on its own is insufficient to meet the auditory demands of infants, which justifies the need for additional interventions, such as music therapy. They, however, reported that they would mainly refer infants with a higher GA to an auditory intervention, which highlights the need for more awareness about the benefits for younger infants (63). Nurses were satisfied with live MT in a feasibility study conducted at the University Medical Center Groningen (110). Generally, live music therapy was preferred over recorded music by Medical personnel as well as parents (47).

4.1 Guidelines for Implementation

There are currently not a lot of frameworks for the implementation of MT with premature newborns (22,89). Regardless of the kind of intervention implemented, proper conduction of MT interventions is necessary to ensure safety and prevent adverse effects, such as overstimulation.
Common prerequisites for all vocal and auditory stimulations are the parents' informed consent and the regular application of therapy sessions in a trustful and quiet atmosphere (22). Implementing MT requires a multidisciplinary approach, under the guidance of a certified music therapist, who is not only educated in the field of MT, but has also acquired knowledge about the normal fetal and neonatal development, and their capability to respond to music as well as the skills to motivate the parents. Ideally, the MT specialist would also participate at rounds with the rest of the medical staff, to ensure complete and continuous exchange of information about the infant (22–24,27,89). The general noise level in the NICU should, according to the American Academy of Paediatrics, not exceed 45dB (89,114).

MT can be initiated based on a referral from the medical staff (89). Indications include physiological instability, dysregulation, and pain in infants. Parental indications include, among others, anxiety, feelings of helplessness, depression, and difficulties with bonding. In isolated cases, end-of-life care can also include MT, especially if requested by the family (22,89).

There are few contraindications, such as extreme or life-threatening instability of the infant, probable overstimulation, parental instability or refusal as well as the use of paralytics, which can increase the auditory perception (22,30).

The minimum age for the implementation of MT remains the subject of discussions. According to Nöcker-Ribaupierre, mild stimulation can be initiated at 25 weeks, while other authors, as well as the American Music Therapy Association. do not recommend MT under the age of 28 GW (24,30,89). The key criterion for music interventions, however, is clinical stability (27,89).

Before the intervention, the therapist needs to obtain detailed information about the infant's stage of development, behavior, sensory and psychosocial needs, as well as their course of disease and prognosis. Additionally, information about the parents, such as their current mental status, should be obtained (24,89).

Ideally, MT should be delivered regularly, two or three times per week throughout the whole hospitalization. They should last 30 minutes and take place in a separate room to allow for privacy and minimize distractions by hospital staff or visitors as well as disturbing other hospitalized infants during their sleep or feeding sessions (89).

Auditory stimuli should follow quiet, simple, and repetitive patterns adjusted to the family's cultural background and the premature infant's age. Infants at different developmental stages have different sensory needs (22,24,27,89). Parents should be encouraged to actively participate in each session and the therapist should continuously re-assess and support the family (22,89).

Infants below 32 weeks should ideally receive stimulation by the maternal or therapist's voice. Towards the end, kangaroo care and careful stimulation by recorded music can be incorporated, but close attention needs to be paid to the infant's signs and cues, such as hiccoughs and tongue protrusions, to avoid overstimulation (24,89,115).

As the infant grows, the interventions can slowly get more complex and transition from simple stimulation with the voice only to the incorporation of touch and some instruments, such as an Ocean disc, Gato box or monochord. Additionally, interactive learning can be enhanced in this stage, for example, by means of multimodal stimulation or the use of PAL to improve non-nutritive sucking (24,89,115).

As for every other intervention in health care, proper documentation of the kind of intervention as well as the infant is important. The infant's vital signs and behavior should be noted and documented before and after each session (89,116).

On average, 160 premature infants are born each year in the Clinical Hospital Center Rijeka. 70% of these infants are born at GW 33 or later, while 30% of infants were born at GW 32 or earlier. Figure 1 shows the number of preterm births according to GA from 2018 to 2023.

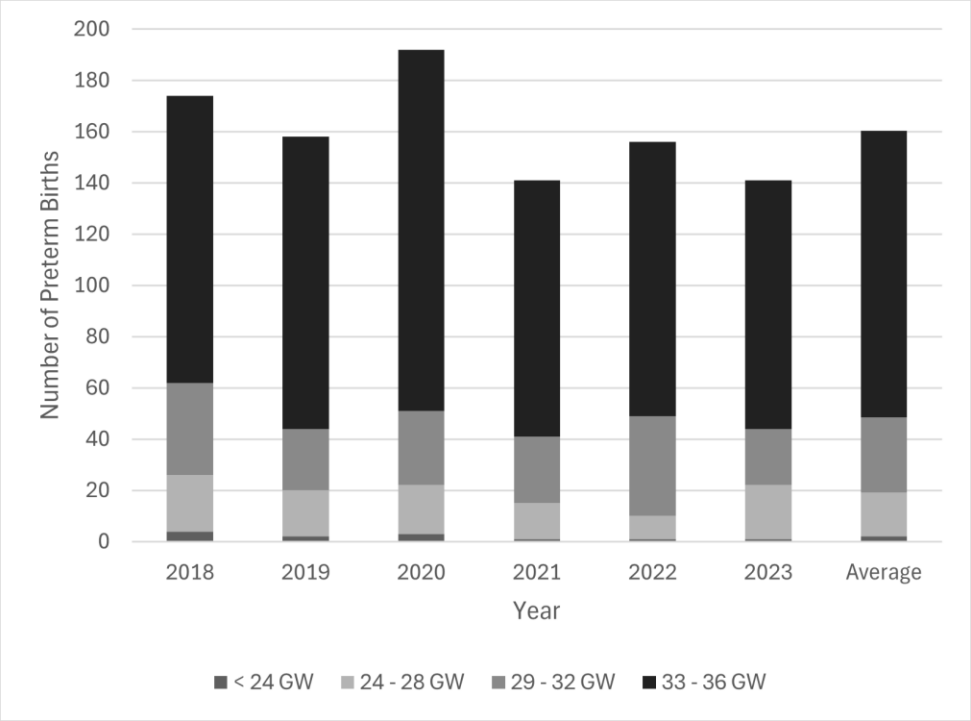

Figure 1: Number of Preterm Births According to Gestational Age per year in KBC Rijeka, 2018-2023

The length of hospitalization and, therefore, the resources needed to implement MT vary. On average, infants born after GW 32 stay in the hospital for two weeks, while infants born before GW 32 are usually discharged at approximately 33 to 34 weeks of corrected gestational age (CGA). For simplification purposes, the average stay in the following calculation will be set to two weeks, since the majority of infants are born after GW 32. Based on the average number of infants born per year, it can be estimated that there are three premature infants born each week if birthdays are distributed evenly. Considering a two-week stay for each infant, there should be approximately six premature infants staying in the NICU per week. The length of a MT session should be around 30 minutes. Considering preparations, documentation, and interaction with the nursing staff and parents, the amount of workload per infant is estimated

to be 60 to 90 minutes per session. Three interventions per week per infant would cause a workload of approximately 27 hours for a music therapist.

The additional costs that would arise due to MT should be weighed against the potential savings due to shorter hospital stays, less tube feeding or less need for analgosedation. A cost-benefit analysis would be needed to explore this possibility in detail. Future research and preparation for implementation could, besides economic analyses, include surveys to assess attitudes and expectations of the KBC staff.

5 Conclusion

In conclusion, the incorporation of MT interventions offers a multidisciplinary approach to neonatal care. It can stabilize premature infants and relieve them from stress and pain during hospitalization, while at the same time accelerating their neurobehavioral development. This does not only facilitate the early development of feeding skills but also seems to have an impact on cognitive abilities years after being discharged from the hospital. Moreover, MT supports parental coping and enhances parent-infant closeness during and beyond the period of separation, highlighting its holistic benefits for the whole family.

MT should be implemented in Croatian NICUs since it is a cost-effective intervention that is, clinically and interpersonally, of high value for infants and parents. Regardless of its influence on physiologic and developmental parameters, it provides moments of normalcy and closeness, thereby improving the quality of life for the whole family. More standardized interventions led by trained specialists and individually tailored to specific groups of infants as well as education of healthcare professionals should be the focus of future clinical research to enable a widespread adoption and impact. Through these efforts, MT can become an indispensable tool in enhancing the quality of care in NICUs.

6 Summary

Music therapy (MT) is increasingly used in medicine. Even the youngest patients, premature infants, and their families can benefit from these interventions. This literature review highlights the physiological and developmental effects of MT on premature infants, exploring its influence on physiological stability, sleep, feeding, pain management and neurodevelopment, while, at the same time, elaborating on parental mental health and bonding. MT interventions adjusted to the NICU environment show promising outcomes on the regulation of infants' heart rates, reduction of pain and stress and facilitating neurobehavioral development. Furthermore, MT can reduce parental stress, anxiety, and depression and strengthen the bond between the parents and their infant.

Despite variable study designs and outcomes, MT is a valuable addition to neonatal care and should be implemented in NICUs to enhance the quality of life of the whole family.

Keywords: Family-Centered Nursing, Integrative Medicine, Music Therapy, Neonatal Intensive Care, Premature Infants

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8 CV

Dana Michele Bode was born on the 28th of June 1998 in Birkenfeld, Germany.

Graduating from secondary school in 2017, she started her medical journey by moving to Rijeka in 2018 and enrolling in the medical faculty.

Her enthusiasm for pediatrics began at an early age. While still in secondary school, she spent her afternoons and weekends babysitting. At the age of 14, she came into contact with medicine for the first time while participating in courses for childcare and first aid for infants and children. She had her first internship in a pediatric ward in Germany. After secondary school, she extended her experience with another month-long internship in a childcare facility.

Throughout her studies, she did diverse internships in various medical areas and looked into alternative medicine. This multifaceted approach helped to broaden her horizon and deepen her understanding of different fields.

In recognition of her academic excellence in the academic year 2022/2023, she received the Dean’s Award.