

O potencial impacto da cronobiologia no cuidado ao recém-nascido em Unidade de Terapia Intensiva Neonatal

The potential impact of chronobiology in the care of newborns in the Neonatal Intensive Care Unit

El potencial impacto de la cronobiología en el cuidado del recién nacido en la Unidad de Cuidados Intensivos Neonatales

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Abstract

Newborns admitted to the Neonatal Intensive Care Unit (NICU) are exposed to care routines and interventions that significantly alter their biological rhythms. These interventions include exposure to irregular or continuous lighting patterns, artificial temperature maintenance, high noise levels, intermittent feeding schedules, mechanical ventilation, administration of medications, and painful or stressful procedures. The aim of this study is to reflect on the impacts resulting from the disruption of biological rhythms in newborns admitted to the NICU and to explore evidence-based strategies to disseminate chronobiological principles and foster clinical practice in this context. The variety of manipulations and environmental changes to which newborns are exposed – often chaotic and conflicting – not only compromises the development of circadian rhythms and the overall health of the newborns, but also negatively influences hospitalization duration, weight gain, and neuroendocrine development. Although the importance of circadian rhythmicity is widely recognized, the care provided to newborns in the NICU has not yet adequately incorporated these principles. In this scenario, the nursing team emerges as a central agent in implementing chronosensitive practices at the bedside to bridge this clinical gap. The need for innovative approaches is evident, with the potential to transform the NICU environment into a space that promotes healthy circadian development.

Resumo

Os recém-nascidos (RN) internados na Unidade de Terapia Intensiva Neonatal (UTIN) são expostos a rotinas de cuidados e intervenções que alteram significativamente seus ritmos biológicos. Tais intervenções incluem a exposição a padrões de iluminação irregulares ou contínuos, manutenção artificial de temperatura, níveis elevados de ruído, horários intermitentes de alimentação, ventilação mecânica, administração de medicamentos e procedimentos dolorosos ou estressantes. O objetivo deste estudo é realizar uma reflexão acerca dos impactos decorrentes da interrupção dos ritmos biológicos em RN internados em UTIN e explorar estratégias baseadas em evidências para divulgar princípios cronobiológicos e fomentar a prática clínica nesse contexto. A variedade de manipulações e mudanças ambientais a que os RN são expostos – frequentemente caóticas e conflitantes – não apenas compromete o desenvolvimento dos ritmos circadianos e a saúde dos RN, mas também influencia negativamente o tempo de hospitalização, o ganho de peso e o desenvolvimento neuroendócrino. Embora a importância da ritmicidade circadiana seja amplamente reconhecida, observa-se que os cuidados destinados aos RN internados na UTIN ainda não incorporam adequadamente esses princípios. Nesse cenário, a equipe de enfermagem emerge como agente central na implementação de práticas cronossensíveis à beira do leito, visando suprir essa lacuna clínica. A urgência por abordagens inovadoras torna-se evidente, com potencial para transformar o ambiente da UTIN em um espaço promotor do desenvolvimento circadiano saudável.

Resumen

Los recién nacidos (RN) ingresados en la Unidad de Cuidados Intensivos Neonatales (UCIN) están expuestos a rutinas de cuidado e intervenciones que alteran significativamente sus ritmos biológicos. Dichas intervenciones incluyen la exposición a patrones de iluminación irregulares o continuos, el mantenimiento artificial de la temperatura, niveles elevados de ruido, horarios intermitentes de alimentación, ventilación mecánica, administración de medicamentos y procedimientos dolorosos o estresantes. El objetivo de este estudio es reflexionar acerca de los impactos resultantes de la interrupción de los ritmos biológicos en los RN ingresados en la UCIN y explorar estrategias basadas en evidencia para difundir los principios cronobiológicos y fomentar la práctica clínica en este contexto. La variedad de manipulaciones y cambios ambientales a los que los RN están expuestos –frecuentemente caóticos y conflictivos– no solo compromete el desarrollo de los ritmos circadianos y la salud de los RN, sino que también influye negativamente en el tiempo de hospitalización, el aumento de peso y el desarrollo neuroendócrino. Aunque se reconoce ampliamente la importancia de la ritmicidad circadiana, se observa que los cuidados destinados a

Keywords

Pediatric nursing; Chronobiology; Biological rhythms; Newborn; Neonatal Intensive Care Unit; Nursing care

Descritores

Enfermagem pediátrica; Cronobiologia; Ritmos biológicos; Recém-nascido; Unidade de Terapia Intensiva Neonatal; Cuidados de enfermagem

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los RN ingresados en la UCIN aún no incorporan adecuadamente estos principios. En este escenario, el equipo de enfermería emerge como agente central en la implementación de prácticas innovadoras al lado del paciente, con el objetivo de suplir esta brecha clínica. La urgencia por enfoques innovadores se hace evidente, con el potencial de transformar el entorno de la UCIN en un espacio que promueva un desarrollo circadiano saludable.

Introduction

Several biological phenomena in living organisms exhibit rhythmicity, characterized by the regular variation of biochemical, metabolic, physiological and behavioral processes.⁽¹⁾ In human physiology, this temporal organization is fundamental and adjusted in 24-hour cycles that regulate everything from molecular functions to sleep-wake patterns.⁽²⁾ Physiological processes that oscillate within a period of approximately 24 hours are known as circadian rhythms.^(2,3) They persist even in the absence of environmental cues, but are usually synchronized by variations in the environment, especially via photic stimuli, e.g. light perceived by the retina,^(1,4) by non-photoc stimuli⁽⁵⁾ and food intake⁽⁶⁾ or deregulated by external signals and the health condition itself.⁽⁷⁻⁹⁾

Circadian rhythms are regulated by the body's internal clock, the suprachiasmatic nucleus (SCN), a structure located in the anterior hypothalamus of the brain. This system integrates environmental cues and coordinates the adaptation of the body's functions.⁽¹⁾ During pregnancy development, the fetus's endogenous rhythms are synchronized by maternal signals generated by its activity-rest cycle, feeding times, body temperature, and cortisol and melatonin levels, among other hormones.^(1,10,11) Throughout pregnancy, the uterine environment provides ideal conditions for fetal development, preparing the developing organism for a successful transition to postnatal life.⁽¹²⁾ This maternal-fetal synchronization is essential to establish robust circadian patterns that will support physiological and adaptive processes in the postnatal period. At this point, it is relevant to mention that changes in neurodevelopment or maturation of the neural/molecular machinery of the internal clock during the postnatal phase can also contribute to the imbalance of biological rhythms in childhood and adulthood.

After birth, the newborn is exposed to environmental light and temperature variations for the first time. Since the structures of their internal timekeeping system are not yet fully developed, newborns remain largely dependent on maternal cues to synchronize

their biological rhythms.⁽¹³⁾ During this critical period of development, the synchronization of biological rhythms occurs through photic cues (such as exposure to environmental light) and non-photoc cues (such as patterns of social interaction, variations in environmental temperature, breastfeeding on demand, and hormones and soluble molecules present in breast milk).⁽¹²⁻¹⁴⁾

In adverse conditions, such as when newborns remain hospitalized in a Neonatal Intensive Care Unit (NICU) due to prematurity or illness, they may be deprived of rhythm synchronization signals normally experienced early in life⁽⁵⁾ or have altered patterns due to the excess of environmental signals that do not oscillate rhythmically. At this point, the considerable improvement in survival rates of newborns in the ICU in recent decades due to advances in support and therapeutic technologies is noteworthy. However, their permanence (especially premature newborns) under care in the NICU for long periods is still common. This place generally does not provide an adequate environment for the development and synchronization of endogenous biological rhythms^(5,15-17) especially due to the lack of adequate light-dark environmental variations, exposure to continuous or irregular light, excessive noise, enteral and parenteral feeding schedules, painful procedures,⁽¹⁸⁾ stressful interventions or excessive physical contact/manipulation, use of medications and irregular sleep-wake patterns.⁽¹⁾ All of this evidence is presented schematically in figure 1.

The neonatal period represents the most vulnerable phase for infant survival. The abrupt transition of newborns from the controlled uterine environment, essential for their development,⁽¹⁵⁾ to the adverse reality of the NICU after birth can result in chronodisruption (instability or irregularity of endogenous rhythms), compromising the establishment of endogenous rhythms and impacting survival in the neonatal period. In addition, this disruption can have lasting repercussions on health and well-being throughout childhood and adulthood.⁽⁵⁾ Despite its relevance to the neonatal health context, the principles of chronobiology are still not fully taught in professional health

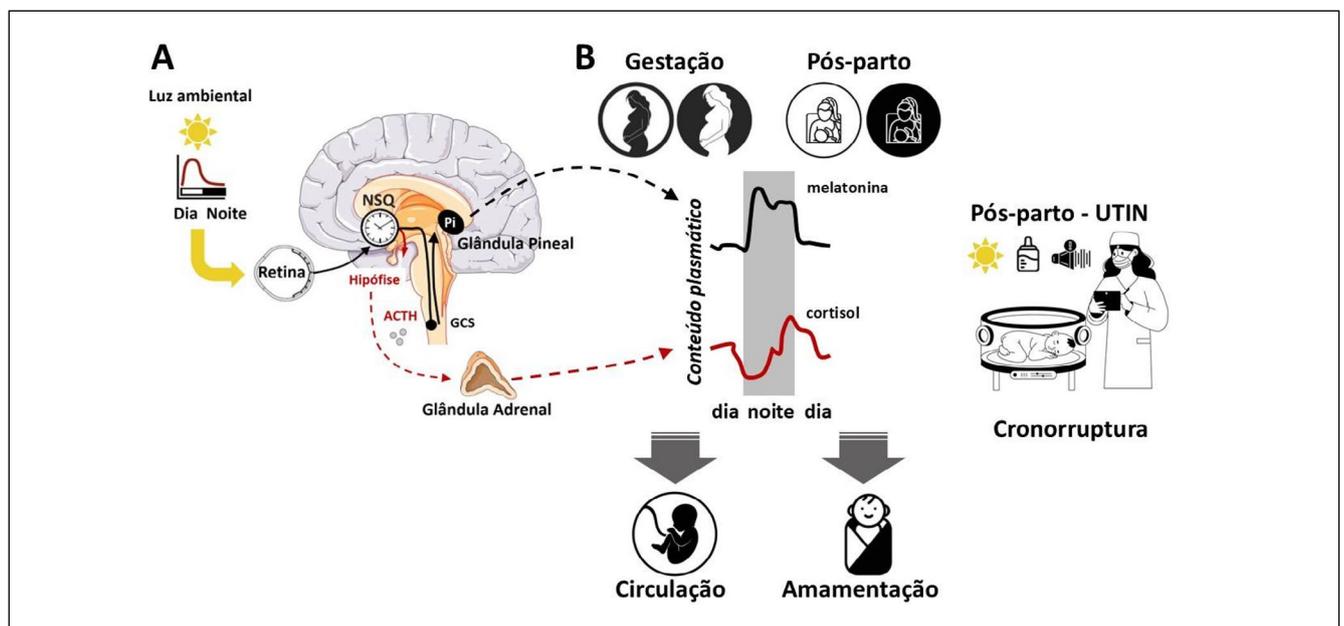
training, nor incorporated into clinical practice. Thus, there is an emerging need for studies and dissemination of evidence that can support an approach to neonatal care and adjustments that promote the homeostasis of physiological processes according to biological time to foster efficient therapy.⁽⁵⁾

In this context, chronosensitive care (integrated through variation between environment and endogenous time) continues to be frequently neglected. There is growing concern that the absence of appropriate temporal cues in the NICU does not favor the adequate development of the circadian system and physiological functions of newborns. Consequently, it is imperative to optimize the NICU environment to promote biological synchronization through the modulation of stimuli – such as photic, auditory and tactile – and the minimization of painful procedures, aiming to reduce disruptive exposures and improve clinical outcomes and future quality of life. Based on this evidence, the aim of the present study is to reflect on the

impacts resulting from the interruption of biological rhythms in newborns admitted to the ICU and explore evidence-based strategies to disseminate chronobiological principles and promote clinical practice in this context.

Artificial lighting in the ICU: Adverse impacts on rhythm synchronization in newborns

Newborns admitted to the NICU are often exposed to continuous artificial lighting throughout the 24 hours of the day, a condition that suppresses the synchrony of the endogenous timekeeping machinery and its biochemical-functional responses, in addition to depriving newborns of the environmental light-dark cycle, which is essential for the regulation of physiological processes. Sensory overload resulting from excessive stimuli – associated with the immaturity of the central nervous system – can also compromise neurophysi-



A) Cyclic variations (day/night) in ambient brightness are perceived by photoreceptors present in the retina that express melanopsin. The projection of photoreception information from the retina to the Suprachiasmatic Nuclei (SCN) via the retinohypothalamic tract synchronizes the oscillatory activity of the genetic machinery present in the neurons of this hypothalamic nucleus. In this way, the presence of light promotes the reset of the transcriptional control of the genes of this machinery and synchronizes the organism to the presence of light in the environment. From this central clock, several internal rhythms are harmonized in synchrony through the endocrine response of the pineal and adrenal glands. The production of melatonin by the pineal gland (PI) is increased during the dark phase via control of the release of noradrenaline from sympathetic postganglionic fibers originating in the superior cervical ganglion (SCG). The central clock also orchestrates the production of corticosteroids via neural control of the pituitary gland and secretion of adrenocorticotropic hormone (ACTH), which acts on the cortex of the adrenal gland via systemic circulation, inducing the production of cortisol. In humans, the cortisol peak occurs at the transition between the dark/light phases and, therefore, precedes the wakefulness phase (waking), while melatonin production at night signals the presence of the dark phase. B) Under physiological conditions during pregnancy, variations in luminosity in the environment integrate the production of melatonin and cortisol hormones to adjust the chronobiology and appropriate development of the fetus via the circulatory system at the maternal-fetal interface. After birth, the adjustment and refinement of the newborn's synchrony occurs via the mammary gland and breastfeeding, where hormones, immune cells and nutrients are transferred by breastfeeding according to the maternal endogenous rhythm. When newborns need to be completely isolated from contact with the maternal rhythm, such as during NICU admission, constant light, enteral or parenteral feeding or milk offered at times other than expressed milk, as well as noise and handling at times not scheduled by the care team, are factors that can influence the misalignment of the newborn's endogenous rhythms (chronodisruption).

Figure 1. Organization of the endogenous timekeeping system and implications for neonatal health

ological processing capacity, exacerbating metabolic risks and behavioral disorganization, such as the sleep-wake cycle.^(5,15)

Current guidelines for lighting in NICUs recommend adjustable ambient levels between 10 lux (equivalent to twilight) and 600 lux (similar to office lighting) with no specific guidelines regarding the duration or spectrum of the light range used.⁽¹⁹⁾ Recent studies highlight that exposure to regular light-dark cycles – in contrast to continuous lighting regimes or prolonged darkness – can act as a critical endogenous synchronizer for neonatal circadian maturation. Comparative studies demonstrate that the implementation of rhythmic lighting in the NICU environment is associated with improvements in physiological and behavioral parameters, such as cardiorespiratory stability, better metabolic adjustment, and organization of sleep patterns.^(15,20,21)

A recent prospective multicenter randomized clinical trial investigated the impact of structured light-dark cycles on newborns.⁽²²⁾ The experimental group was exposed to daytime lighting (275.8 ± 14 lux; 07:00–19:00) and nighttime darkness (<25 lux; 19:00–07:00), while the control group maintained continuous light (275.8 ± 14 lux daytime and 145.3 ± 14 lux nighttime).⁽²²⁾ Newborns in the photoperiod-structured protocol had an 18.7% greater weight gain (15.2 ± 2.1 vs. 12.8 ± 1.9 g/kg/day) and 18% fewer days of hospitalization (28.3 ± 3.2 vs. 34.5 ± 4.1 days), indicating that circadian synchronization promotes improved energy metabolism in critically ill neonates. Other recent evidence indicates that the implementation of light-dark cycles in NICUs is associated with better clinical outcomes in premature newborns, including metabolic stability and reduced postnatal complications.⁽¹⁵⁾ On the other hand, studies have reinforced that exposure to continuous lighting in these units delays the maturation of neonatal circadian rhythms, compromising the regulation of processes such as the secretion of the hormone melatonin, which is produced by the pineal gland only at night and is essential for adjusting the sleep-wake cycle in childhood.^(9,23) Furthermore, significant day-night variation in melatonin levels was observed in newborns exposed to structured light cycles and absent in those under constant lighting.⁽²²⁾

Despite the benefits, preserving nocturnal darkness in the NICU faces practical challenges, such as

the constant need for continuous monitoring and the implementation of clinical care. To balance these demands, innovative strategies – such as the use of protective glasses and incubators equipped with adaptive lighting systems – have been tested with moderate success, ensuring clinical safety and minimizing negative outcomes, such as chronodisruption.^(21,23)

Even with recent advances, persistent methodological limitations – such as sample heterogeneity in relation to maternal health status, type of delivery and birth weight, as well as lack of standardization in light parameters (intensity, spectrum and photoperiod) and uncontrolled confounders (e.g., use of sedatives or phototherapy) – reinforce the need for randomized longitudinal studies with rigorous control groups.^(15,22) In general, the implementation of light rhythmicity in NICUs appears to be a promising intervention to modulate circadian rhythms, favoring the development and endogenous secretion of endocrine pathways in the fetus and the consolidation of rhythmic physiological functions in an age-appropriate manner.^(21,23) As a practical guideline, the implementation of circadian light protocols emerges as a viable strategy to replicate the observed benefits and should be part of public policies for care in intensive care units.

Chrononutrition: Breastfeeding and its influence on rhythm synchronization in newborns

As previously presented, during pregnancy the fetus is exposed to the mother's endogenous rhythms, which are responsible for regulating the baby's physiological, metabolic and behavioral essential processes for intra-uterine development. After birth, this synchronization is interrupted, and the newborn becomes dependent on external temporal cues, mainly those transmitted via breast milk that also have a biochemical composition varying rhythmically.^(11,24) In this sense, there is a maternal-neonatal interdependence that continues to occur even after birth. Isolating this connection through hospitalization in a NICU requires active interventions to mitigate the potential disruptive effects that would not occur in a proper natural course.

Breast milk is composed of several components such as lipids, proteins, carbohydrates and macronutrients such as vitamins, and also has a range of cellular

components that favor the immunological maturation of the newborn, in addition to hormone content such as glucocorticoids and melatonin equivalent to those present in the maternal circulation. These contents are passively transferred from the maternal plasma to the secretion of milk via the mammary glands, exposing the newborn to hormonal oscillations synchronized with the maternal endogenous rhythm.⁽²²⁾ Therefore, they present marked daily variations in their concentration, with significantly higher levels of tryptophan and melatonin at night, compared to the daytime period.⁽²⁴⁾

In hospital settings such as the NICU, neonatal enteral feeding (expressed breast milk or formula) is generally administered at regular intervals (e.g., every 3 hours), following protocols based on birth weight, gestational age and postnatal age without temporal adjustments or quantitative variations according to the light-dark cycle. This practice results in continuous exposure to nutrients, ignoring the circadian variation inherent to what is needed in each hour of the day and for neonatal development.⁽²⁴⁾ Furthermore, recent studies highlight that expressed breast milk can act as an endogenous synchronizer, since its biochemical composition – depending on the hormone content present in the mother at the time of collection – can adjust the newborn's rhythms.^(12,24)

Administering breast milk in a manner that is not synchronized with daily light and dark cycles to which the newborn admitted to the NICU should be exposed can compromise the synchronization of physiological processes, such as the maturation of the hypothalamic-pituitary-adrenal axis and the regulation of the sleep-wake cycle. A very relevant example is the concentration of melatonin in breast milk, which peaks between midnight and 4 am, reflecting the circadian synthesis of this hormone by the maternal pineal gland at night.⁽²²⁾ Infants fed with infant formula or breast milk expressed during the day and offered at night have significantly reduced or nonexistent serum melatonin levels.⁽²⁴⁾ Thus, evidence has reinforced that preserving the temporality of expressed milk (e.g., immediate collection and offering of breast milk) is associated with better metabolic stability and a reduction in clinical complications, such as gastrointestinal disorders and immune dysfunctions.^(15,22) Considering the immaturity of the neonatal timekeeping system, evidence has also indicated that preserving the natural

rhythmicity of breast milk should be considered at the time of feeding in the NICU – where milk expressed during the day (e.g., 6 am-6 pm) is offered during this phase the following day, or that food offered at night (e.g. 6pm-6am) comes from milk expressed in the same period.

Previous studies have observed that maintaining this temporal strategy is associated with significant improvements in the organization of the sleep-wake cycle, including reduced sleep latency and increased REM sleep duration.^(22,24) In contrast, in addition to the adverse environment for the synchrony of the newborn's endogenous rhythms, the random administration of expressed milk at different times of the day has great potential to induce chronodisruption of its physiological functions, especially in the desynchronization of the hypothalamic-pituitary-adrenal axis and fragmented sleep patterns.⁽¹²⁾ This generally uncontrolled practice in the NICU environment is supported by the literature and has already been described as being correlated with a higher risk of metabolic disorders, such as transient hyperglycemia and feeding intolerance, particularly in preterm newborns.^(21,24)

Therefore, the precise definition of the chronobiological role of breast milk in the NICU environment lacks incorporation into clinical practice, despite its relevance as a critical synchronizer in the postnatal period. Evidence indicates that most NICUs maintain feeding protocols that ignore the temporal variation in breast milk composition, failing to align nutritional supply with the endogenous rhythms of the newborn.⁽²⁵⁾ Synchronizing breastfeeding with biological rhythms requires accurate labeling of the milk expression time, allowing chronological administration that respects the temporal variability of its composition, combined with the education of mothers and teams about the relevance of these patterns in neonatal development.

Chronosensitive Neonatal Care

The integration of chronobiology into neonatal care requires coordinated multidisciplinary approach with joint action in the translation of scientific knowledge and implementation of evidence-based clinical protocols. The implementation of chronosensitive care – based on the modulation of endogenous rhythm

synchronizers, such as structured light-dark cycles and temporal synchronization of feeding – is associated with significant impacts on neonatal growth and neurodevelopment. These interventions have broad implications, extending beyond critically ill newborns in NICUs.

The absence of light variation between phases of the day in NICUs contrasts with evidence linking the reduction of nighttime light to better clinical outcomes (psychomotor development, sleep and weight gain). However, its implementation is hampered by the lack of robust clinical trials and adapted infrastructure, reflecting gaps in clinical practice, especially in highly complex settings.⁽²⁵⁾ This challenge arises from the fact that the lighting environment in the NICU is inherently difficult to control. In part, this results from the fixed position of incubators in relation to windows and the need for bright light for both planned and unplanned care activities at any time of day.

Noise reduction practices also stand out as critical interventions in NICUs, where sound levels (70–90 decibels) exceed international recommendations (≤ 45 decibels).^(26,27) Excessive nighttime noise is associated with sleep deprivation and neonatal chronodisruption, compromising the stability of sleep phases.⁽²⁸⁾ Mitigation strategies include: use of ear protectors with the potential to reduce stress, continuous mon-

itoring of sound levels, behavioral modification of the care team, and implementation of local protocols (Figure 2). Despite advances, the scarcity of studies on noise-circadian rhythmicity interactions, as well as the lack of standardization limit the adoption of evidence-based practices, requiring robust clinical trials for environmental optimization.

Conclusion

Humanizing the NICU requires integrating the principles of chronobiology into care in order to respect the biological rhythms established during pregnancy, birth, and hospital discharge with the aim to optimize neurobehavioral development and prevent repercussions in childhood and adult life. In this context, nursing stands out as a transformative agent by reviewing protocols and implementing evidence-based practices such as synchronizing light cycles, chronoregulated breastfeeding, and reducing disruptive interventions through strategies that contribute to mitigating circadian desynchronization. Theoretical and practical advances are also proposed, including longitudinal studies on early chronodisruption, interdisciplinary training of the team, and adaptation of hospital infrastructure, aiming to create environments that foster less artificial environments.

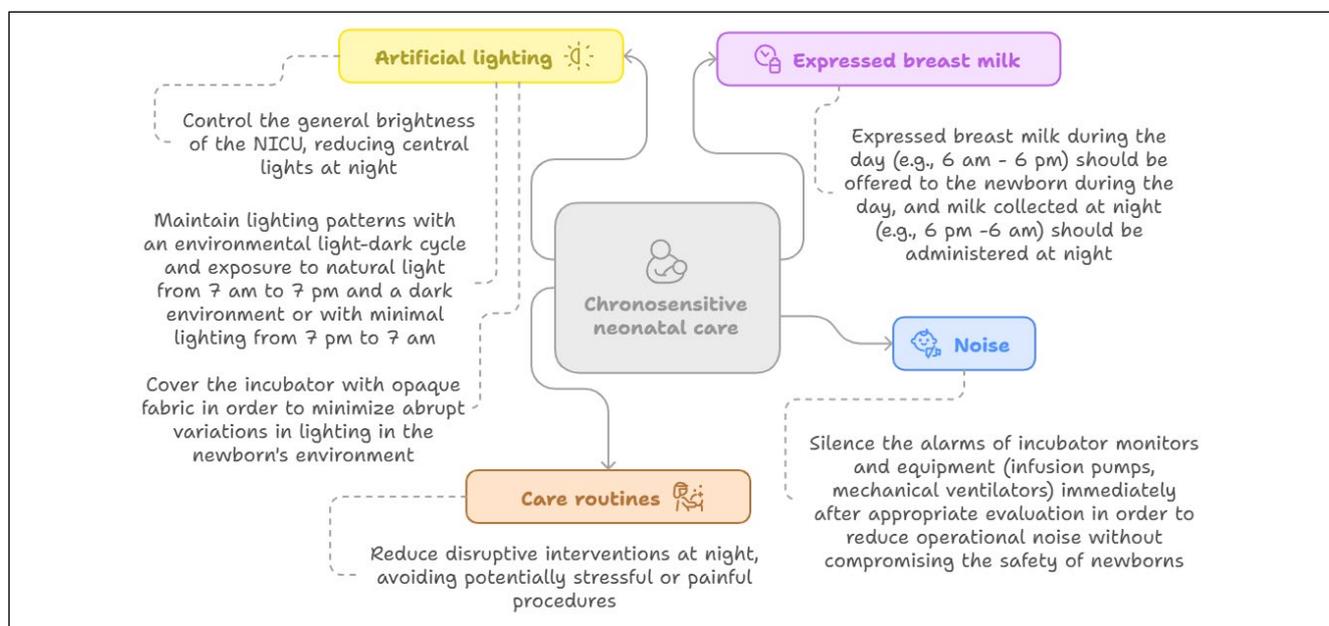


Figure 2. Practical recommendations for chronosensitive care in the NICU

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