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Epigenetic Modifications Induced by Neonatal Intensive Care Unit Environments in Newborns: A Narrative Review

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ABSTRACT

Context: The Neonatal Intensive Care Unit (NICU) environment exposes newborns, particularly preterm and Very Low Birth Weight (VLBW) infants, to stressors such as mechanical ventilation, artificial lighting, and nutritional challenges, potentially inducing epigenetic modifications like Deoxyribonucleic Acid (DNA) methylation and histone alterations. These changes may impact long-term neurodevelopmental and metabolic outcomes.

Evidence Acquisition: This review searched Scopus, Google Scholar, and PubMed using keywords "epigenetic modifications," "NICU," "newborn," "DNA methylation," and "preterm infant." No time limits were applied, and only English-language full-text articles were included. Additional terms like "VLBW infants" were used to expand results.

Findings: NICU stressors, including hypoxia and nutritional deficits, were linked to DNA methylation and histone modifications in genes tied to neurodevelopment and immunity in preterm infants. Interventions like optimized nutrition and stress reduction showed potential to mitigate these epigenetic changes.

Conclusion: NICU environments induce epigenetic modifications, affecting newborn health. Advanced technologies, such as CRISPR-based epigenome editing and single-cell epigenomics, alongside tailored interventions, may reduce adverse outcomes. Further research is needed to standardize protocols and assess long-term effects.

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Introduction

The Neonatal Intensive Care Unit (NICU) environment, essential for the survival of preterm and very low birth weight (VLBW) infants, introduces various stressors such as mechanical ventilation, hypoxia, oxidative stress, artificial lighting, and nutritional challenges. These stressors may induce epigenetic modifications, including DNA methylation and histone modifications, altering gene expression related to neurodevelopment, immunity, and metabolism [1]. Globally, an estimated 13-15 million preterm births occur annually, with many requiring NICU care [2]. In Iran, the prevalence of preterm birth is approximately 9-10%, varying by region [3]. NICU-induced epigenetic changes may contribute to long-term issues like cognitive impairments or metabolic disorders, affecting a significant number of neonates worldwide [4]. Strategies to mitigate these effects include optimizing NICU conditions, such as providing nutritional support and reducing stress [5]. Screening based on gestational age and birth weight helps identify at-risk infants [6]. Maternal and neonatal factors, like nutritional deficiencies, are key contributors to epigenetic alterations [7]. Recent studies emphasize that NICU-related stressors, including oxidative stress, influence DNA methylation and histone acetylation, necessitating advanced interventions [8].

Literature Search and Selection

Relevant literature was searched in Scopus, Google Scholar, and PubMed using the keywords “epigenetic modifications,” “NICU,” “newborn,” “DNA methylation,” “histone modification,” and “preterm infant.” No strict time restrictions were applied, and only English-language full-text articles were prioritized. Initial searches yielded limited results, so additional terms like “preterm neonate” and “VLBW infants” were included to broaden coverage. Studies were selected based on their relevance to epigenetic changes in NICU-admitted newborns, including randomized controlled trials (RCTs), cohort studies, and systematic reviews. Manual screening of titles/abstracts and full texts was performed for relevance. Two independent reviewers assessed the abstracts. Excluded were non-English articles, reviews without primary data on epigenetics, animal studies, and studies not focusing on NICU-related stressors in human newborns.

Results

The literature search identified several hundred articles across the selected databases. After screening titles, abstracts, and full texts for relevance, six key studies providing direct evidence of NICU-related stressors and epigenetic modifications (primarily DNA methylation) in human preterm or very low birth weight (VLBW) infants were selected for detailed review. These studies, comprising observational cohorts, longitudinal designs, and a scoping review, reflect the emerging nature of this field and focus predominantly on stress-regulation genes. The main findings from these studies are summarized in Table 1.

Malin et al. (2023): A scoping review synthesizing multiple cohorts found consistent associations between NICU toxic stress (such as procedural pain and morbidities) and DNA methylation changes in NR3C1, SLC6A4, and HSD11B2, which are linked to neurodevelopmental vulnerability [9].

Nist et al. (2024): Cumulative NICU exposure in preterm infants was associated with DNA methylation variation in stress-related genes, resulting in altered neurobehavioral profiles [10].

Hodge et al. (2024): Very preterm infants showed differential DNA methylation patterns related to early adversity, predicting long-term developmental risks [11].

van Dokkum et al. (2023): Neonatal stress and pain exposure in extremely preterm infants led to methylation changes in SLC6A4 and NR3C1, contributing to impaired stress regulation [12].

Provenzi et al. (2018): Early NICU stress caused epigenetic alterations in stress-response genes across preterm/VLBW cohorts, with potential socio-emotional impacts [13].

Lester et al. (2019): Longitudinal follow-up revealed persistent NR3C1 and SLC6A4 methylation changes after cumulative NICU stress, associated with increased neurodevelopmental risks [14].

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Overall, NICU stressors are consistently linked to DNA methylation alterations in HPA axis (NR3C1) and serotonin system (SLC6A4) genes, with implications for stress regulation and neurodevelopment. The limited number of primary studies underscores the need for larger, longitudinal research.

Table 1: Studies examining epigenetic modifications in NICU-admitted newborns

Study	Design	Sample Description	Key Findings
Malin et al. (2023) [9]	Scoping review	Synthesis of multiple cohorts	Associations between NICU-related toxic stress and DNA methylation changes in NR3C1, SLC6A4, and HSD11B2
Nist et al. (2024) [10]	Cohort	Preterm infants	DNA methylation variation in stress-related genes associated with altered neurobehavioral profiles
Hodge et al. (2024) [11]	Cohort	523 very preterm infants	Differential DNA methylation patterns linked to early life adversity
van Dokkum et al. (2023) [12]	Cohort	Extremely preterm infants (initial cohort n = 45)	Methylation changes in SLC6A4 and NR3C1 associated with neonatal stress and pain exposure
Provenzi et al. (2018) [13]	Review of cohorts	Preterm / VLBW cohorts	Epigenetic alterations in stress-response genes with implications for socio-emotional development
Lester et al. (2019) [14]	Longitudinal	NICU stress-exposed infants	Persistent methylation changes in NR3C1 and SLC6A4 associated with increased neurodevelopmental risk

Discussion

The six key studies reviewed provide converging evidence that NICU stressors induce epigenetic modifications, predominantly DNA methylation changes in stress-regulation genes such as NR3C1 and SLC6A4, in preterm newborns [15]. These findings underscore the remarkable sensitivity of the developing epigenome to the intensive care environment, where life-saving interventions paradoxically introduce significant early-life adversity.

Malin et al. (2023), through a comprehensive scoping review, synthesized data from multiple cohorts and identified consistent associations between NICU toxic stress-including procedural pain and medical morbidities- and altered DNA methylation in NR3C1, SLC6A4, and HSD11B2. This synthesis highlights a reproducible pattern across studies, linking epigenetic variation to increased neurodevelopmental vulnerability [9].

Recent primary investigations further support these observations. Nist et al. (2024) demonstrated that cumulative NICU exposure in preterm infants correlates with DNA methylation variation in stress-related genes, resulting in altered neurobehavioral profiles [10]. Similarly, Hodge et al. (2024), in a large cohort of 523 very preterm infants, reported differential DNA methylation patterns associated with early adversity, with implications for long-term developmental trajectories [11].

Van Dokkum et al. (2023) provided direct evidence in extremely preterm infants, showing that neonatal stress and pain exposure drive methylation changes in SLC6A4 and NR3C1, contributing to impaired stress regulation- a critical pathway for later emotional and behavioral outcomes [12].

Conceptual and longitudinal perspectives reinforce the persistence of these effects. Provenzi et al. (2018) described an "epigenetic footprint" from early NICU stress on stress-response genes, with potential socio-emotional consequences [13]. Lester et al. (2019) extended this by documenting persistent NR3C1 and SLC6A4 methylation changes following cumulative NICU stress, associated with increased neurodevelopmental risks into later childhood [14].

Mechanistically, increased methylation of SLC6A4 disrupts serotonergic signaling, reduces synaptic plasticity and contributes to socio-emotional dysregulation and cognitive challenges. NR3C1 methylation alterations interfere with glucocorticoid receptor expression, dysregulate the HPA axis, and promote chronic stress vulnerability,

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which may increase risks for anxiety, attention deficits, and neurodevelopmental disorders [16].

Cumulative exposure to pain, morbidities, and early adversity consistently correlates with differential DNA methylation patterns, as shown in recent cohorts and syntheses [17]. The persistence of these changes into infancy and beyond highlights potential lasting impacts on stress regulation and behavior [18].

Nutritional support providing methyl donors (e.g., folate, zinc) and DHA, combined with developmental care interventions such as kangaroo care, shows preliminary promise in buffering adverse epigenetic effects, though direct causal evidence in human NICU settings remains limited [19]. These strategies are particularly important for preterm infants with immature regulatory systems that offer little intrinsic buffering capacity [20].

Limitations

The included studies often involve small to moderate cohorts (ranging from 28 to 523 infants), many from single centers, limiting generalizability. Variability in NICU protocols, stressor measurement, and epigenetic assessment methods hinders direct comparisons. The primary focus on DNA methylation may overlook histone modifications, non-coding RNA, and other epigenetic mechanisms. Restriction to English-language publications and the high cost of epigenetic profiling in resource-limited settings further constrain the evidence base. The emerging nature of the field, with only a limited number of primary human studies available, highlights the need for caution in interpretation. To address these issues, future research should prioritize multicenter longitudinal studies, standardized protocols, inclusion of diverse global populations, and broader multi-omics approaches. Overall, while the field is emerging, the consistency across independent cohorts strengthens confidence in the association between NICU stressors and epigenetic reprogramming of stress pathways, with clear implications for long-term health [21, 22-24]. Evidence from animal models indicates that early-life stress can lead to transgenerational epigenetic inheritance through altered DNA methylation and non-coding RNAs, affecting stress responses and metabolic traits in subsequent generations [15, 17]. Limited human studies, primarily from severe trauma cohorts, suggest possible intergenerational transmission of stress-related marks in glucocorticoid pathway genes [19]. At present, there is no direct evidence linking NICU-specific stressors to transgenerational effects in humans. However, if such mechanisms are demonstrated, they could have important public health implications by potentially influencing susceptibility to neurodevelopmental and stress-related disorders across generations, underscoring the need for long-term, multigenerational follow-up studies.

Conclusion

NICU environments induce epigenetic modifications, particularly DNA methylation changes in stress-related genes (NR3C1 and SLC6A4), which may influence long-term neurodevelopmental and stress regulation outcomes in preterm infants. Optimized nutrition, stress reduction strategies, and standardized care protocols offer practical mitigation approaches. Continued multicenter research with advanced epigenetic monitoring is essential to validate these associations, refine interventions, and improve long-term health for NICU graduates.

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Conflict of interest

There is no conflict of interest.

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