REVIEW ARTICLE

Advancing Neonatal Outcomes: Erythropoietin in Preterm Care

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Abstract

Background:
Preterm birth remains a significant global health challenge, contributing to high rates of neonatal mortality and long-term neurodevelopmental impairment. Despite advancements in neonatal intensive care, effective pharmacologic strategies for neuroprotection in preterm infants are limited. Recombinant human erythropoietin (rhEPO), traditionally used for anemia of prematurity, has shown potential neuroprotective effects due to its anti-apoptotic, anti-inflammatory, and neurotrophic properties.

Objective:
To systematically review the current evidence from randomized controlled trials (RCTs) and meta-analyses on the efficacy and safety of erythropoietin in improving neurodevelopmental outcomes in preterm neonates.

Methods:
A comprehensive literature search was conducted across PubMed and Frontiers databases for RCTs and meta-analyses published between 2020 and 2024. Inclusion criteria were English-language studies assessing neurodevelopmental outcomes following rhEPO therapy in preterm infants. Studies lacking full-text access, non-RCT design, case reports, or involving non-preterm populations were excluded. Data extraction focused on sample size, rhEPO dosage, administration protocols, and primary neurodevelopmental outcomes.

Key Results:
Among six included studies (four RCTs, one meta-analysis, one post hoc analysis), findings varied significantly. High-dose rhEPO administered early in life did not reduce the risk of severe neurodevelopmental impairment or death at two or five years of age in large trials. However, in selected subgroups, such as preterm infants with intraventricular hemorrhage, low-dose rhEPO showed significant improvements in combined outcomes of mortality and neurological disability. Cognitive gains associated with iron supplementation in rhEPO-treated infants were noted but not conclusively linked to rhEPO alone.

Conclusion:
Current evidence does not uniformly support rhEPO as an effective neuroprotective agent for the broader preterm population. While selective benefit is noted in high-risk groups, heterogeneity in study designs and outcomes limits generalizability. Further multicenter trials with standardized protocols and long-term follow-up are essential.

Keywords:
Erythropoietin, Preterm infants, Neurodevelopment, Neuroprotection, Intraventricular hemorrhage, Randomized controlled trials

INTRODUCTION

Preterm birth, defined as delivery before 37 weeks of gestation, remains a major global health challenge, contributing significantly to neonatal morbidity and mortality. It is categorized into distinct subgroups based on gestational age: **extremely preterm** (<28 weeks), **early preterm** (<34 weeks), and **late preterm** (between 34 weeks 0 days and 36 weeks 6 days).(1) Determining the precise gestational age is essential for obstetric decision-making and neonatal management. First-trimester ultrasound remains the gold standard for accurate dating, whereas second- and third-trimester scans carry slightly wider margins of error. When antenatal records are lacking or uncertain, neonatal gestational age can also be estimated postnatally using scoring systems such as the New Ballard Score, although this is less reliable in sick neonates.(2) Despite advances in neonatal care leading to higher survival rates, 40–50% of very preterm infants still experience developmental delays. This often results in long-term academic and cognitive challenges.(3)

The burden of preterm birth is significant worldwide. Approximately one in ten births globally occur before 37 weeks, with even higher rates observed in low-resource countries like India, where preterm delivery accounts for around 13% of all births.(4) Despite this, advancements in neonatal care have substantially improved outcomes. Survival of very preterm infants (born before 32 weeks) has exceeded 90–95% in many tertiary care centers, while outcomes for infants born at the edge of viability around 22 to 25 weeks are steadily improving due to enhanced respiratory support and neuroprotective strategies.(5)

Preterm birth is a multifactorial condition with a complex interplay of biological, environmental, genetic, and social determinants. While some preterm births are medically indicated to preserve maternal or fetal health, such as in cases of preeclampsia, fetal growth restriction, or placental abruption, many occur spontaneously without a clearly identifiable cause. Spontaneous preterm labor often results from premature activation of pathways involved in normal parturition, including uterine contractions, cervical ripening, and rupture of fetal membranes.
A variety of maternal conditions have been implicated in increasing the risk of preterm birth. These include **uterine overdistension**, **cervical insufficiency**, and **decidual or placental dysfunction**. Inflammatory responses in the reproductive tract, often triggered by **infections** such as bacterial vaginosis, chorioamnionitis, or sexually transmitted infections, are significant contributors. Moreover, **environmental exposures**—including tobacco smoke, air pollution, heavy metals, and endocrine-disrupting chemicals—have also been associated with higher preterm birth rates.

Nutritional factors such as **low maternal BMI**, **micronutrient deficiencies**, and **poor dietary diversity** further compound the risk.

Genetics also plays a crucial role in the predisposition to preterm labor. Family history and studies of twin pregnancies suggest a heritable component, and recent advances in genomics have identified several gene-environment interactions. However, results are often inconsistent across populations. The **maternal microbiome** is another emerging area of interest; imbalances in the vaginal or placental microbiota may influence inflammatory pathways and contribute to early labor onset.

In preterm infants, neurological impairments often result from the interruption of critical stages of brain development that normally take place during the third trimester. These include the rapid growth of neurons, formation of synaptic connections, and the development of myelin. When birth occurs prematurely, these processes are abruptly halted, making the underdeveloped brain more susceptible to damage. Cells responsible for producing myelin, known as oligodendrocytes, along with the delicate blood vessels in the brain, are particularly vulnerable. As a result, affected infants may experience long-term difficulties in movement, cognition, and sensory integration.(6). Although early interventions can enhance outcomes, there is a notable lack of pharmacological therapies specifically developed for neuroprotection in these preterm neonates.(3)

Several factors contribute significantly to brain damage in premature infants. These include hypoxia and ischemia, intraventricular hemorrhage, free radicals and antioxidants are the combined factors resulting in enduring consequences such as cerebral palsy, cognitive impairments, and behavioral issues. These effects frequently persist into adulthood, negatively impacting quality of life and academic performance.(6)

Recombinant human erythropoietin (rhEPO), a hormone commonly used to treat anemia in preterm infants, has demonstrated potential neuroprotective properties. Beyond its hematopoietic role, EPO crosses the blood–brain barrier and interacts with EPO receptors on neurons, astrocytes, oligodendrocytes, and microglial cells. Activation of these receptors initiates anti-apoptotic and anti-inflammatory signaling pathways such as JAK2/STAT5, PI3K/Akt, and MAPK/ERK that contribute to cellular survival, reduce oxidative damage, and modulate cytokine release. These pathways are vital during early brain development, especially in preterm infants exposed to hypoxic-ischemic injury.(7)

Preclinical studies, including those reviewed by Perrone et al(7), show that rhEPO enhances

oligodendrocyte maturation, promotes myelination, stabilizes the blood–brain barrier, and fosters angiogenesis. These biological actions have been associated with reduced cerebral lesion size and improved cognitive and motor function in animal models. (8,9)

Clinically, these mechanisms provide a strong rationale for exploring rhEPO in the management of white matter injury and delayed neurodevelopment in preterm neonates. Thus understanding these molecular mechanisms strengthens the therapeutic plausibility of rhEPO in neonatal neuroprotection. While erythropoietin is primarily studied for neuroprotection, recent evidence highlights its wider physiological benefits and safety in preterm infants. It has long been used to treat anemia of prematurity, reducing the need for transfusions and related risks like infection and iron overload. By boosting erythropoiesis, rhEPO improves oxygen delivery, which may indirectly aid neurodevelopment. Some studies suggest rhEPO may also support cardiovascular stability by influencing vascular tone and endothelial function, though data in neonates are limited. Importantly, adverse effects such as polycythemia, hypertension, or thrombosis have not been significantly increased in most trials, indicating a favorable safety profile.

Consequently, rhEPO has emerged as a promising candidate for neonatal neuroprotection. Recent clinical trials report improved white matter integrity and reduced incidence of cerebral palsy and other neurodevelopmental disorders. These findings reinforce rhEPO's potential as a multifunctional therapeutic agent in preterm infant care. (3)

Other Efforts of Erythropoietin (rhEPO)

1. **Cardioprotective Effect**:
   Beyond its role in erythropoiesis, erythropoietin has been observed to exert protective effects on cardiac tissue, particularly under conditions of reduced oxygen supply. Experimental models suggest that EPO helps prevent heart cell death and promotes repair through activation of cell survival signaling pathways, such as PI3K/Akt. These properties may offer benefit during episodes of ischemia and reperfusion injury. (9,10)

2. **Angiogenesis and Wound Healing**:
   EPO contributes to angiogenesis by stimulating endothelial proliferation and mobilizing progenitor cells. Through **VEGF modulation**, it enhances tissue repair in ischemic and damaged regions.(7)

3. **Hematopoiesis and Anemia Management** :

   One of the most established uses of rhEPO in neonatology is for treating anemia of prematurity. By stimulating the bone marrow to produce red blood cells, it reduces the need for transfusions, thereby lowering the risks of transfusion-related complications such as infections and iron overload.(11–13)

4. **Potential Risks of rhEPO Therapy**

   Hypertension and Thromboembolism: Administration of high doses of rhEPO may elevate hematocrit levels, which can increase blood viscosity and resistance, potentially leading to high blood pressure or clot formation. While these effects are more commonly reported in adults, they remain relevant in neonatal safety assessments. (14,15)

   Tumor Progression (Experimental Concern):

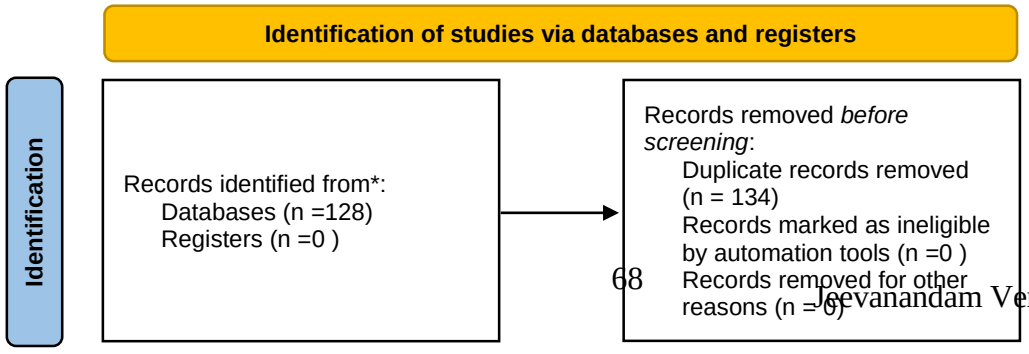
   Preclinical findings suggest that EPO may promote growth in tumors that express EPO receptors. Though this risk is not established in neonatology, long-term surveillance is recommended..(8,16)

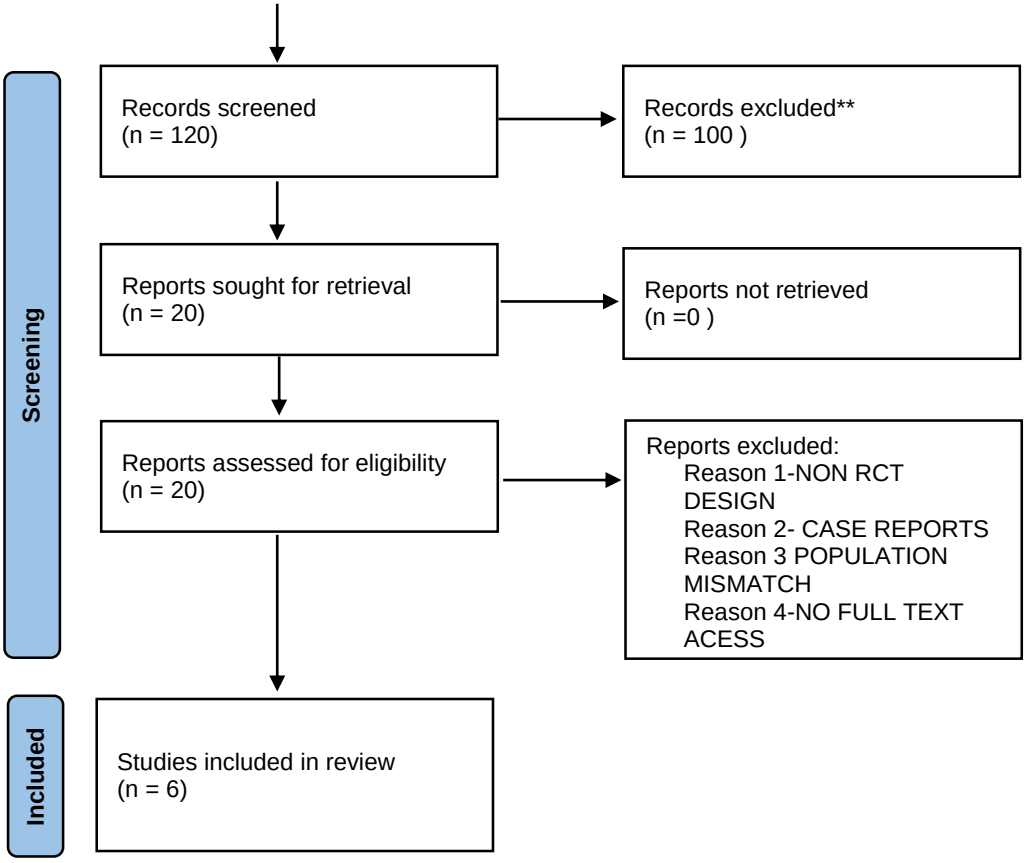
This summary aimed to review the multifaceted impact of prematurity on neurodevelopment highlighting the role of rhEPO in mitigating these challenges.

METHODOLOGY

To review the neuroprotective effects of erythropoietin (rhEPO) in preterm neonates, we conducted a comprehensive literature search focusing on randomized controlled trials (RCTs) and meta-analyses published between 2020 and 2024. The primary databases utilized were PubMed and Frontiers. Search terms included "erythropoietin," "neuroprotective therapy," "preterm neonates," "randomized controlled trial," and "meta-analysis," combined using Boolean operators to refine the search results.

Inclusion criteria encompassed studies published within the specified timeframe, available in English, and reporting on neurodevelopmental outcomes following rhEPO administration in preterm infants.





Exclusion criteria ruled out non-randomized studies, case reports, reviews without original data, studies focusing on populations other than preterm neonates, and articles not accessible in full text. Titles and abstracts identified through the search were screened for relevance, followed by full-text assessments against the inclusion and exclusion criteria. Data extraction focused on study design, sample size, rhEPO dosing regimens, outcomes measured, and key findings related to neuroprotection. The methodological quality of included RCTs was evaluated based on randomization, blinding, and completeness of follow-up, while meta-analyses were assessed for the comprehensiveness of literature search, inclusion criteria, and data synthesis methods. This systematic approach ensured a thorough and unbiased synthesis of current evidence regarding the neuroprotective role of EPO in preterm neonates. The final review included a total of six studies, comprising four randomized controlled trials, one meta-analysis, and one post hoc analysis derived from an RCT.

LITERATURE REVIEW:

A randomized, double-blind, multicenter trial investigated the neuroprotective effects of high-dose erythropoietin (rhEPO) in extremely preterm infants, enrolling 941 neonates born between 24 weeks and 27 weeks 6 days of gestation. Infants were randomized to receive either Epo or placebo

within 24 hours of birth, with the rhEPO group receiving 1000 U/kg intravenously every 48 hours for six doses, followed by 400 IU/kg subcutaneously three times per week until 32 weeks postmenstrual age. The primary outcome death or severe neurodevelopmental impairment by 22 to 26 months of postmenstrual age was observed in 26% of infants in both the rhEPO and placebo groups (relative risk: 1.03; 95% confidence interval: 0.81–1.32; P=0.80), showing no significant difference. Secondary outcomes, including rates of retinopathy of prematurity, intracranial hemorrhage, sepsis, necrotizing enterocolitis, bronchopulmonary dysplasia, death, or serious adverse events, were also similar between groups. The study concluded that high-dose rhEPO treatment initiated within 24 hours of birth and continued through 32 weeks postmenstrual age did not reduce the risk of severe neurodevelopmental impairment or death at 2 years of age.(11)
A study involving 316 eligible infants, with 157 in the recombinant human erythropoietin (rhEPO) group and 159 in the placebo group, evaluated the effects of rhEPO on outcomes in preterm infants with intraventricular hemorrhage (IVH). While there were no statistically significant differences in mortality ($p = 0.176$) or neurological disability rates ($p = 0.055$) between the two groups at 18 months of corrected age, significantly fewer infants in the rhEPO group experienced poor outcomes (combined death and neurological disability): 14.9% vs. 26.4% (odds ratio [OR] 0.398; 95% confidence interval [CI] 0.199–0.796; $p = 0.009$). Additionally, the incidence of Mental Development Index scores below 70 was lower in the rhEPO group compared to the placebo group (7.2% vs. 15.3%; OR 0.326; 95% CI 0.122–0.875; $p = 0.026$). These findings suggest that repeated low-dose rhEPO treatment can improve outcomes in preterm infants with IVH.(17)
An analysis of 692 infants (355 placebo, 337 rhEPO) examined the relationship between iron supplementation and neurodevelopmental outcomes. On day 60, enteral iron intake ranged from 0 to 14.7 mg/kg/day (IQR 2.1–5.8 mg/kg/day), with an average of 3.6 mg/kg/day in the placebo group and 4.8 mg/kg/day in the rhEPO group. A significant positive association was found between iron dose at 60 days and cognitive scores on the BSID-III, with a 50 mg/kg increase in cumulative iron dose linked to an improvement of 0.77 points ($P = .03$). Although higher iron doses were associated with better motor and language outcomes, these findings did not reach statistical significance, and results at 90 days showed no significant effects. Importantly, the cognitive effect size was consistently greater in infants treated with rhEPO compared to placebo. These findings suggest that increased iron supplementation in preterm infants, particularly those receiving rhEPO, may positively influence cognitive development.(18)

A randomized clinical trial investigated the long-term neurodevelopmental effects of early high-dose recombinant human erythropoietin (rhEPO) administration in very preterm infants. The study enrolled 448 infants born between 26 and 31 weeks of gestation, who were randomly assigned to

receive either rhEPO or a placebo within 3 hours of birth. The primary outcome assessed was the composite of death or severe neurodevelopmental impairment at 5 years of age. The results indicated no significant difference between the rhEPO and placebo groups in the primary outcome, with 11.5% of children in the rhEPO group and 11.0% in the placebo group experiencing death or severe neurodevelopmental impairment (risk difference, 0.5% [95% CI, −5.5% to 6.5%]; adjusted odds ratio, 1.05 [95% CI, 0.61 to 1.80]; P = .86). Additionally, no significant differences were observed in secondary outcomes, including cognitive, motor, and language development. The study concluded that early high-dose rhEPO treatment did not reduce the risk of death or severe neurodevelopmental impairment at 5 years of age in very preterm infants.(14)

An extensive meta-analysis involving 23,894 preterm infants from 106 randomized controlled trials assessed the effectiveness of various interventions for preventing retinopathy of prematurity (ROP). Among the 21 interventions analyzed, erythropoietin (rhEPO) administration emerged as an important preventive strategy. Compared to placebo and several other approaches, early administration of rhEPO demonstrated notable effectiveness in reducing the occurrence of ROP, although its overall efficacy was slightly less pronounced than vitamin A supplementation, which ranked highest. Vitamin A supplementation was identified as having the strongest preventive effect, yet the results concerning erythropoietin are particularly noteworthy. rhEPO 's neuroprotective properties, alongside its role in angiogenesis regulation, may contribute to its beneficial outcomes in reducing ROP incidence. Despite promising results, uncertainties remain about the optimal dosage, timing, and long-term effects of rhEPO administration in preterm infants. This analysis underscores erythropoietin’s potential as an effective measure against ROP, emphasizing the need for further targeted studies. Clarifying these aspects through future research could enhance clinical guidelines, improving outcomes for preterm infants at risk of developing ROP.(7)

A randomized clinical trial evaluated whether early high-dose recombinant human erythropoietin (rhEPO) influences behavioral outcomes and health-related quality of life (HRQoL) in very preterm infants. Among 448 infants born between 26 and 32 weeks’ gestation, 228 were randomized to receive RHEpo, and 220 received a placebo within 48 hours of birth. At approximately 5 years of age, 317 children (71%) had questionnaire data available for analysis. Results showed no significant differences between the RHEpo and placebo groups in behavioral difficulties (mean score: 8.41 vs. 7.76; P = .37) or in any HRQoL domains assessed. The trial concluded that prophylactic administration of high-dose rhEPO did not improve behavior or quality of life outcomes at 5 years of age in children born very preterm.(14)

Although many studies have investigated erythropoietin (rhEPO) as a neuroprotective agent in preterm infants, the results have been inconsistent. Several factors likely contribute to these differences. One major variable is dosing: some trials, like Song et al. (2021)(17), used lower doses

(500 IU/kg every other day for two weeks), while others, such as the PENUT trial by Juul et al. (2020)(11), used high-dose regimens with maintenance therapy. The timing of rhEPO initiation whether within hours or days of birth and the duration of treatment also vary widely, affecting outcomes.

Differences in patient populations further complicate comparisons. Studies may include infants with or without intraventricular hemorrhage (IVH), span a range of gestational ages, and involve diverse baseline health risks. Methodological differences, including how randomization is performed, which neurodevelopmental tools are used (e.g., BSID-III versus KABC), and how long participants are followed (from 18 months to 5 years), make it difficult to draw uniform conclusions.

Moreover, some studies include additional therapies, like iron supplementation, which as shown by German et al. (2021)(18) can influence cognitive outcomes and confound rhEPO's independent effects. These inconsistencies highlight the need for standardized protocols and more uniform study populations to accurately assess rhEPO's role in neuroprotection among preterm infants.

Clinical Themes Emerging from Current Literature

1. **High-Dose vs. Low-Dose Efficacy**

A large, multicenter randomized controlled trial (PENUT) enrolled 941 extremely preterm infants (born between 24 and 27 weeks + 6 days) to evaluate the effects of high-dose erythropoietin (rhEPO).(11) Infants in the treatment arm received 1000 IU/kg intravenously every 48 hours for six doses, followed by 400 IU/kg subcutaneously three times weekly until 32 weeks postmenstrual age. The primary outcome—death or severe neurodevelopmental impairment (NDI) at 22 to 26 months—showed no difference between the rhEPO and placebo groups (26% each; relative risk 1.03; 95% CI: 0.81–1.32; P = 0.80).

In contrast, a smaller trial by Song et al. assessed the impact of low-dose rhEPO (500 IU/kg IV every other day for two weeks) in 316 preterm infants diagnosed with intraventricular hemorrhage (IVH). Although mortality and disability rates were not individually significant, the combined outcome of death or neurological disability was significantly reduced in the rhEPO group (14.9% vs. 26.4%, OR 0.398; P = 0.009).(17)

High-dose rhEPO failed to demonstrate clear neuroprotective advantages in large trials. However, selective use of low-dose rhEPO in high-risk populations such as those with IVH may offer specific benefit.

2. Mortality, Neurodevelopment, and Cognitive Outcomes

The PENUT trial reported no significant improvements in mortality or NDI with rhEPO.(11) Similarly, Natalucci et al. followed 448 very preterm infants for five years and found no benefit of early high-dose rhEPO in reducing death or severe impairment.(14)

In a post hoc analysis of the PENUT cohort (n = 692),(11) German et al.(18) found a positive association between cumulative enteral iron intake at 60 days and improved cognitive scores at 2 years. Infants in the rhEPO group received more iron and had slightly higher BSID-III cognitive scores (P = 0.03). However, effects on motor and language domains were not significant.

The consistent lack of improvement in long-term outcomes suggests limited efficacy of rhEPO in reducing mortality or severe impairment. While enhanced iron intake in the rhEPO group may influence cognitive development, its independent effect remains unclear.'

3. IVH-Specific Effects

Among preterm infants with IVH, rhEPO demonstrated a more favorable outcome profile. In the Song et al. trial, fewer infants in the rhEPO group had Mental Development Index scores below 70 compared to placebo (7.2% vs. 15.3%; OR 0.326; P = 0.026).(17)

These findings suggest that targeted administration of rhEPO may be beneficial in neonates with pre-existing brain injury, such as IVH.

4. Short-Term Versus Long-Term Benefits

Short-term improvements were reported in select studies. Song et al. observed improved composite outcomes in IVH cases, and German et al. linked higher iron exposure to improved cognitive scores at 2 years. However, long-term evaluations—including Natalucci's 5-year follow-up and HRQoL assessments—did not support sustained neurodevelopmental gains.(17,19)

Early neurodevelopmental improvements observed in short-term follow-up may not be sustained over time. This limits the long-term applicability of rhEPO as a neuroprotective agent.

Table 1: Summary of the observations from the published articles

Study	Sample Size	rhEPO Dose & Schedule	Primary Outcomes	Key Findings

Song et al. (2021)(17)	N=316	500 IU/kg IV every other day × 2 weeks	Death or neurological disability at 18 mo	↓ combined poor outcomes (14.9% vs 26.4%, p=0.009)
Juul et al. (2020) - PENUT(11)	N=941	1000 IU/kg IV × 6 doses then 400 IU/kg SC TID till 32 wks PMA	Death or severe NDI at 22–26 mo	No sig. diff. in primary outcome (26% vs 26%, p=0.80)
Natalucci et al. (2020)(14)	N=450	3000 IU/kg at 0, 12–18, 36–42 hrs	Cognitive performance (KABC) at 5 yrs	No benefit in IQ at 5 yrs
Perrone et al. (2022) - Review(7)	26 RCTs reviewed	500–3000 IU/kg various regimens	Neurodevelopment, HIE, stroke	Heterogeneous; need better dose tailoring
German et al. (2021) - Iron & EPO (PENUT)(18)	N=692 (post hoc from PENUT)	As per PENUT dosing protocol	BSID-III cognitive scores at 2 years	↑ Iron dose positively correlated with cognitive scores esp. in Epo group
Ream & Lehwald (2018) - Neurologic Review(6)	Narrative Review	Not applicable	Neurodevelopmental impairments by imaging and follow-up	Preterm birth linked to long-term structural and functional impairments

Despite encouraging findings, several limitations are evident across the reviewed studies. A key issue is the variation in sample sizes, with some RCTs enrolling small cohorts that limit the ability to detect subtle effects or rare adverse events. For instance, Song et al. (2021)(17) included 316 infants, while the larger PENUT trial by Juul et al. (2020)(11) involved 941, affecting generalizability. Additionally, inconsistency in outcome measures such as differing neurodevelopmental scales (Bayley-III, KABC, MDI) and assessment timings makes comparisons and meta-analyses challenging. Variations in rhEPO dosing and treatment duration further complicate interpretation of efficacy and safety. While a few trials evaluated long-term neurodevelopment, others relied on short-term surrogate markers. These limitations highlight the need for standardized protocols and long-term, multicenter studies to better assess rhEPO 's role in preterm care.

CONCLUSION

- Erythropoietin shows potential in improving outcomes in select groups of preterm infants, particularly those with intraventricular hemorrhage.
- Current research lacks uniformity in dosing regimens, assessment tools, and follow-up timelines, making interpretation difficult.
- The benefit of rhEPO in reducing mortality or severe neurodevelopmental impairment in the broader preterm population remains unproven.
- Positive short-term outcomes have not consistently translated into long-term neurodevelopmental gains.
- Future studies should implement uniform treatment protocols and standardized outcome measures to allow comparison across trials.
- Larger, multicenter randomized controlled trials are needed to evaluate efficacy in diverse clinical settings.
- Long-term follow-up into later childhood is necessary to fully understand the impact of rhEPO on cognitive, motor, and behavioral development.
- Until stronger evidence is available, rhEPO therapy should be considered experimental and restricted to well-designed clinical studies under close monitoring.

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