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Review Paper

Effectiveness of Lutein Supplementation in Reducing Morbidity and Mortality in Preterm Infants

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ABSTRACT

Background: Preterm infants are born with deficient antioxidant systems and miss the crucial third trimester transfer of lutein and zeaxanthin. These carotenoids protect the retina and brain from oxidative stress. This deficiency contributes to major neonatal morbidities, including retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), and intraventricular hemorrhage (IVH). This narrative review aimed to evaluate the efficacy and safety of postnatal combined lutein and zeaxanthin supplementation in preterm infants, focusing on its impact on neonatal morbidity and mortality.

Materials and Methods: A structured narrative synthesis of peer-reviewed literature from 2000 to 2025 was conducted. The primary evidence source was the 2025 Cochrane Systematic Review, which included five randomized controlled trials (RCTs) with 666 preterm infants.

Results: Supplementation appeared safe and well-tolerated short-term; however, long-term safety remains unestablished, and the sample size was insufficient to detect rare adverse events. The Cochrane meta-analysis reported a probable reduction in severe ROP (risk ratio [RR] 0.49, 95% confidence interval [CI], 0.29%, 0.81%; moderate-certainty evidence). No significant effects were observed for any-stage ROP, mortality, IVH, necrotizing enterocolitis (NEC), BPD, or sepsis. All evidence derives from combined lutein and zeaxanthin, preventing isolation of individual carotenoid effects.

Conclusion: Combined lutein and zeaxanthin supplementation appears safe in the short term and likely reduces severe ROP. However, long-term safety remains unestablished, and cautious interpretation is warranted. Current evidence shows no benefit for other major morbidities or mortality. Large-scale RCTs with extended follow-up and systematic safety monitoring are urgently needed before routine clinical adoption.

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Introduction

Preterm birth accounts for approximately 10% of live births worldwide and remains a leading cause of neonatal morbidity and mortality [1]. Oxidative stress, driven by supplemental oxygen, inflammation, and immature antioxidant systems, contributes to major complications, such as retinopathy of prematurity (ROP) (the leading cause of preventable childhood blindness), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), and sepsis [2].

Lutein and zeaxanthin are xanthophyll carotenoids that accumulate preferentially in the retina and brain, where they quench reactive oxygen species, filter blue light, and modulate inflammation [3]. Preterm infants miss the bulk of third-trimester placental transfer of these carotenoids and receive suboptimal amounts from breast milk or formula [4]. Pharmacokinetic studies confirmed good oral absorption in preterm neonates [5]. Supplementation trials began in the early 2000s, with pilot studies on safety and antioxidant capacity (2010–2011) followed by clinical outcome randomized controlled trials (RCTs) through 2024 [6].

This narrative review examines postnatal combined lutein and zeaxanthin supplementation exclusively in preterm infants and its impact on morbidity and mortality, drawing on peer-reviewed literature from 2000 to 2025. As a narrative synthesis, this review does not perform independent meta-analysis or quantitative data pooling but rather summarizes and contextualizes findings from high-quality systematic reviews and individual RCTs.

Materials and Methods

Study design

This manuscript was a narrative review of the literature. Given that the primary evidence source was a single high-quality cochrane systematic review with meta-analysis, we did not perform an independent quantitative synthesis or preferred reporting items for systematic reviews and meta-analyses (PRISMA)-guided systematic review. Instead, we conducted a structured narrative synthesis to summarize, contextualize, and interpret the available evidence on lutein and zeaxanthin supplementation in preterm infants.

Search strategy

A structured narrative synthesis was conducted using English-language RCTs, systematic reviews, and meta-analyses identified through PubMed, Scopus, Google Scholar, Cochrane Library, and related databases 2000 - 2025. Search terms included “lutein,” “zeaxanthin,” “preterm infants,” “ROP,” “morbidity,” and “mortality.”

Eligibility criteria

The inclusion criteria focused on studies reporting clinical outcomes (ROP, IVH, NEC, BPD, mortality, and adverse events) in infants <37 weeks’ gestation. Non-randomized designs, term-infant data, and prenatal-only interventions were excluded.

Data sources and synthesis

The 2025 Cochrane review (search date 2024) served as the primary evidence source because of its rigorous methodology and GRADE-assessed certainty [7, 8]. We did not perform an independent risk-of-bias assessment, study selection procedure, or quantitative meta-analysis, as these were already comprehensively conducted within the cochrane review. Additional supporting studies provided context on mechanisms, pharmacokinetics, and earlier findings.Findings are presented narratively with supporting tabular data.

Results

The 2025 Cochrane review included five RCTs (n=666 preterm infants, primarily <32–34 weeks’ gestation or very low birth weight) conducted in Italy and the USA [7, 8]. All trials compared combined lutein+zeaxanthin versus placebo or no supplementation. Dosing ranged from 0.14–0.5 mg lutein daily (with trace zeaxanthin), initiated within the first week of life and continued until neonatal intensive care unit (NICU) discharge or 36 weeks postmenstrual age. Most studies had low risk of bias for randomization, blinding, and allocation concealment. Lutein was never evaluated in isolation. Earlier key RCTs included:

1) Manzoni et al. (2013; multicentre, Italy; n≈200): 0.14 mg lutein+0.0006 mg zeaxanthin daily; well tolerated but no significant reduction in threshold ROP, NEC, or BPD [8]. 2) Dani et al. (2012): No effect on ROP or discharge outcomes [9]. 3) Romagnoli et al. (2010–2011): Demonstrated absorption and antioxidant effects but limited clinical impact on ROP [10].

A 2020 meta-analysis of three RCTs (n=406) confirmed no consistent reduction in ROP incidence, BPD, sepsis, NEC, or mortality [11]. Supporting pharmacokinetic and mechanistic studies (2000–2020) documented low baseline carotenoid levels in preterm infants, good oral bioavailability, and increased biological antioxidant potential with supplementation [12-15].

Effects on ROP

The 2025 Cochrane meta-analysis (four studies, 532 infants) reported:

1) any-stage ROP: Risk ratio (RR) 0.90 (95% confidence interval [CI], 0.66%, 1.24%; I^2=0%; moderate-certainty evidence) — little or no effect [7]. 2) severe ROP (stage≥3): RR 0.49 (95% CI, 0.29%, 0.81%; P=0.005; I^2=0%; moderate-certainty evidence) — probable clinically meaningful reduction [7].

Earlier individual trials and the 2020 meta-analysis showed non-significant trends toward reduced progression to threshold disease [11, 16]. No data on long-term visual impairment were available.

Effects on other morbidities and mortality

1) Mortality (during NICU stay): RR 0.95 (95% CI, 0.42%, 2.17%; four studies, 470 infants; low-certainty evidence) [7]. 2) IVH (all grades): RR 0.87 (95% CI, 0.44%, 1.75%; four studies, 483 infants; low-certainty evidence) [7]. 3) NEC (Bell's stage ≥II): RR 0.87 (95% CI, 0.43%, 1.76%; five studies, 666 infants; low-certainty evidence) [7].

No consistent benefits were observed for BPD or sepsis in pre-2025 data [8, 9, 11, 17]. Observational studies linked higher lutein status to improved neurodevelopmental markers, but supplementation trials have not yet demonstrated statistically significant reductions in these broader outcomes [18, 19]. Across all studies, lutein/zeaxanthin supplementation was well tolerated with no reported adverse events, including skin discoloration, ocular toxicity, or interference with feeding [7, 8, 20].

Safety

Across all studies, lutein/zeaxanthin supplementation was well tolerated in the short term (during NICU stay) with no reported adverse events, including skin discoloration, ocular toxicity, or interference with feeding [7, 8, 20]. Nevertheless, this finding must be interpreted with caution, as the total sample of 666 infants is insufficient to detect rare adverse events, and no long-term safety data beyond the neonatal period are available.

Across all studies, combined lutein/zeaxanthin supplementation was well tolerated in the short term (during the neonatal period) with no reported adverse events, including skin discoloration, ocular toxicity, or interference with feeding [8, 9, 21]. However, several important caveats must be acknowledged: 1) the total sample of 666 infants is insufficient to detect rare adverse events; 2) no long-term safety data beyond the neonatal period are available; 3) follow-up durations in all included trials were limited to NICU discharge or 36 weeks postmenstrual age; and 4) potential effects on neurodevelopment, visual maturation, or other organ systems cannot be assessed from current evidence.

Discussion

The biological rationale for combined lutein/zeaxanthin supplementation is robust: preterm infants exhibit markedly lower retinal and brain carotenoid concentrations than term infants, and these compounds directly protect photoreceptors and reduce systemic oxidative damage [21, 22]. The moderate-certainty evidence for reduced severe ROP aligns with animal models and human observational data [23]. Nevertheless, it is essential to emphasize that while short-term tolerance appears favorable, long-term safety remains entirely unknown. The absence of effect on overall ROP incidence or other major morbidities likely reflects limited statistical power for rarer outcomes, heterogeneity in gestational age, and co-administration of lutein with zeaxanthin (precluding isolation of individual effects) [24]. Evidence remains confined to high-income settings; generalizability to low- and middle-income countries is unknown. Critically, no studies have evaluated outcomes beyond the neonatal period, and the potential for delayed adverse effects—particularly on neurodevelopment, visual function, or metabolic pathways—cannot be assessed from current data. Long-term neurodevelopmental and visual follow-up data are absent, representing a critical gap given lutein's role in brain maturation [25].

Compared with the 2020 meta-analysis, the 2025 Cochrane update incorporates additional trials and refined GRADE assessments, strengthening conclusions for severe ROP while confirming modest overall impact [7, 11]. The limitations of the evidence base include a modest total sample size, variable dosing formulations, and lack of cost-effectiveness analyses.

Future research should prioritize large, international, multi-center RCTs with standardized severe-ROP definitions, systematic safety monitoring, including adverse event reporting, long-term outcomes (e.g. visual acuity at 2 years, Bayley scales), and evaluation of lutein-fortified human-milk fortifiers or preterm formula [7, 26, 27]. In particular, long-term safety surveillance is critical before routine clinical adoption can be considered. Optimal dosing and timing of initiation remain key unresolved challenges that require systematic investigation through dose-finding studies and pharmacokinetic-pharmacodynamic modeling. Additionally, studies evaluating lutein in isolation (without zeaxanthin) are required to determine the independent contribution of each carotenoid.

Limitations

The evidence base has several important limitations. First, as a narrative review, this manuscript does not provide independent PRISMA-guided systematic review methodology, including study selection procedures, quality assessment, or quantitative synthesis. We relied on the rigorous methodology of the Cochrane Review for these elements. Second, the absence of long-term safety data—particularly neurodevelopmental and visual outcomes beyond infancy—represents a major limitation that warrants particular emphasis. While short-term tolerance appears favorable, lutein's role in brain maturation and its biological activity across multiple organ systems suggest that potential effects—both beneficial and adverse—may only become apparent with prolonged follow-up. The lack of post-discharge safety surveillance means that the current evidence base is insufficient to rule out late-onset adverse effects. Third, the total sample of 666 infants is insufficient to detect rare adverse events, and no trials have evaluated supplementation beyond the neonatal period. Fourth, the modest total sample size limits statistical power for rarer outcomes such as mortality and severe IVH. Fifth, variable dosing formulations across studies (0.14–0.5 mg lutein daily) and lack of standardized severe-ROP definitions complicate meta-analysis and clinical translation. Sixth, the absence of cost-effectiveness analyses and the restriction of all included trials to high-income settings limit generalizability. Seventh, and critically, all evidence pertains to combined lutein and zeaxanthin supplementation; the independent effect of lutein cannot be determined from the available data.

Future research should prioritize large, international, multi-center RCTs with standardized severe-ROP definitions, long-term outcomes (e.g. visual acuity at 2 years, Bayley scales), and evaluation of lutein-fortified human-milk fortifiers or preterm formula. Optimal dosing and timing of initiation remain key unresolved challenges that require systematic investigation through dose-finding studies and pharmacokinetic-pharmacodynamic modeling. Additionally, studies evaluating lutein in isolation (without zeaxanthin) are required to determine the independent contribution of each carotenoid.

Conclusion

Postnatal combined lutein and zeaxanthin supplementation in preterm infants appears safe in the short term based on available trial data. It probably reduces the incidence of severe ROP, offering a promising adjunctive strategy for retinal protection. No short-term adverse events were reported in the included trials; however, this observation must be interpreted with considerable caution given: 1) the modest total sample size (n=666), which is insufficient to detect rare adverse events; 2) the absence of any long-term safety data beyond NICU discharge; and 3) the lack of neurodevelopmental follow-up. Therefore, long-term safety remains entirely unestablished.

However, current evidence indicates little or no effect on any-stage ROP, IVH, NEC, BPD, or mortality. It must be emphasized that all available evidence derives from combined lutein and zeaxanthin supplementation; no data exist on lutein alone. Furthermore, the safety profile remains incompletely characterized, and routine clinical adoption cannot be recommended without rigorous long-term safety data. The optimal dose and timing of supplementation remain to be determined, and further large-scale trials with extended neurodevelopmental follow-up and systematic adverse event monitoring are urgently needed before routine clinical adoption can be recommended.

Ethical Considerations

Compliance with ethical guidelines

This manuscript is a review article and does not involve any human or animal studies; therefore, ethical approval is not required.

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Authors' contributions

Formal analysis, methodology, project administration, supervision, writing the original draft: Reza Saeidi; Funding acquisition: Mohammad Kordkatouli; Conceptualization, investigation and data curation, resources, validation, visualization, review and editing: All authors.

Conflicts of interest

The authors declared no conflicts of interest.

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