

Research Article

Long-Term Neurodevelopmental Outcomes Following Early Hormonal Intervention in Congenital Hypothyroidism: A Randomized Controlled Follow-Up Study in Pakistan.

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Abstract: Congenital hypothyroidism is a preventable cause of long-term neurodevelopmental impairment, yet optimal timing and dosing of early hormonal replacement remain debated. This randomized controlled follow-up study evaluated the neurodevelopmental outcomes of infants who received high-initial-dose levothyroxine within the first seven days of life compared with those receiving standard-dose initiation. A total of 120 neonates diagnosed through newborn screening were randomly allocated into early-high-dose (10–12 µg/kg/day) or standard-dose (7–8 µg/kg/day) groups and followed prospectively for five years. Neurodevelopment was assessed using the Bayley Scales at 12 and 24 months, and Wechsler Preschool scales at 5 years. Results demonstrated significantly higher cognitive composite scores in the early-high-dose group at both two years (mean 98.4 ± 12.6 vs 90.7 ± 11.8 , $p = 0.003$) and five years (mean IQ 102.1 ± 10.2 vs 93.8 ± 11.4 , $p = 0.001$). Motor outcomes also showed moderate improvement, while language scores revealed the greatest between-group divergence. Early biochemical normalization correlated strongly with higher cognitive performance ($r = 0.48$, $p = 0.001$). Findings indicate that initiating higher-dose levothyroxine within the first neonatal week may enhance long-term neurodevelopment in congenital hypothyroidism, highlighting the critical importance of early hormonal optimization and sustained developmental monitoring.

Introduction: Congenital hypothyroidism represents one of the most common endocrine disorders identified through newborn screening programs worldwide. Thyroid hormones exert essential

roles in neuronal differentiation, synaptogenesis, myelination, and cortical maturation during fetal and early postnatal life. Disruptions to thyroid hormone availability during this critical window can have lasting impacts on neurocognitive functions, emphasizing the necessity of early therapeutic intervention. The primary goal of treatment is to rapidly normalize serum thyroid-stimulating hormone and free thyroxine levels to support optimal neurological development.¹⁻⁴

Research over the past decade has focused on refining the parameters of therapy, particularly the initial levothyroxine dose and the timing of treatment initiation. Although current guidelines recommend commencement within the first two weeks of life, emerging findings suggest that treatment initiated even earlier—preferably within the first week—may further improve neurodevelopmental outcomes. Moreover, evidence indicates that early high-dose regimens result in more rapid biochemical normalization compared with standard dosing, potentially offering neurological benefits. However, concerns persist regarding overtreatment, risk of hyperthyroxinemia, and its unclear long-term neurobehavioral implications.⁵⁻⁸

Longitudinal studies have demonstrated that subtle cognitive and language deficits persist in some treated children despite biochemically adequate management, indicating that therapeutic optimization remains incomplete. Variability in outcomes has been attributed to differences in etiology, adherence, socioeconomic status, and precise timing of hormonal normalization. Furthermore, neurodevelopmental trajectories appear particularly sensitive to early hormonal levels, underscoring the need to evaluate whether altering initial therapy parameters can modify long-term developmental pathways.⁹⁻¹²

Despite increasing interest in early high-dose strategies, data from low- and middle-income regions remain limited. Environmental, nutritional, and healthcare-access factors may influence both treatment response and neurodevelopment, necessitating context-specific evidence. Pakistan, with established newborn screening coverage expanding gradually, provides an important setting to explore treatment optimization. A randomized controlled follow-up design offers an opportunity to generate rigorous evidence regarding the comparative neurodevelopmental outcomes of early high-dose versus standard-dose levothyroxine initiation.

This study investigates long-term neurodevelopmental performance at five years in children who received different early hormonal regimens for congenital hypothyroidism. By examining cognitive, motor, and language outcomes alongside biochemical normalization patterns, the research seeks to clarify whether early intensified treatment confers sustained neurological benefits. The findings aim to inform treatment protocols, refine dosing strategies, and emphasize the significance of early developmental surveillance.

Methodology: This randomized controlled follow-up study enrolled neonates diagnosed with congenital hypothyroidism through newborn screening at a children's hospital in Gujranwala, a tertiary care centre. Diagnosis was based on elevated TSH values confirming primary hypothyroidism. Sample size was calculated using Epi Info software assuming a medium effect size in cognitive outcomes, 80% power, 95% confidence level, and a 10% attrition allowance, resulting in a target sample of 120 infants.

Infants were randomly allocated into two groups using a computer-generated sequence. The early-high-dose group received levothyroxine at 10–12 µg/kg/day initiated within seven days of birth, while the standard-dose group received 7–8 µg/kg/day initiated within the same timeframe. Inclusion criteria encompassed full-term and late-preterm neonates diagnosed within the first week of life, absence of major congenital anomalies, and parental willingness to engage in long-term follow-up. Exclusion criteria included central hypothyroidism, severe perinatal asphyxia, chromosomal disorders, or metabolic diseases affecting neurodevelopment. Verbal informed consent was obtained from parents after explanation of study aims and follow-up requirements.

Biochemical monitoring occurred at baseline, two weeks, one month, and then every two months during the first year, followed by quarterly assessments. Serum TSH and fT4 levels guided dose adjustments. Developmental assessments were performed at 12 and 24 months using the Bayley Scales, and at five years using the Wechsler Preschool and Primary Scale. Examiners were blinded to treatment allocation. Sociodemographic data were recorded to account for potential confounders.

Data analysis employed SPSS software. Continuous variables were expressed as means ± standard deviation. Between-group differences in developmental scores were analyzed using independent

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t-tests. Associations between biochemical normalization time and neurodevelopment were assessed using Pearson correlation. Statistical significance was set at $p < 0.05$.

Results

Table 1. Baseline Demographic and Clinical Characteristics

Variable	Early-High-Dose (n=60)	Standard-Dose (n=60)	p-value
Birth weight (kg)	2.90 ± 0.42	2.87 ± 0.40	0.71
Gestational age (weeks)	38.1 ± 1.5	37.9 ± 1.4	0.52
TSH at diagnosis (mIU/L)	42.5 ± 11.2	43.1 ± 10.8	0.76
fT4 at diagnosis (pmol/L)	8.2 ± 2.5	8.4 ± 2.3	0.63

Table 2. Neurodevelopmental Scores at 24 Months

Parameter	Early-High-Dose	Standard-Dose	p-value
Cognitive composite score	98.4 ± 12.6	90.7 ± 11.8	0.003
Language composite score	96.1 ± 13.2	88.3 ± 12.5	0.006
Motor composite score	94.7 ± 11.0	89.2 ± 10.7	0.02

Table 3. Five-Year Cognitive and Language Outcomes

Parameter	Early-High-Dose	Standard-Dose	p-value
Full-scale IQ	102.1 ± 10.2	93.8 ± 11.4	0.001
Verbal IQ	101.4 ± 11.9	92.1 ± 12.7	0.002
Performance IQ	100.2 ± 10.7	95.3 ± 11.1	0.04

Explanation:

Children treated with early-high-dose levothyroxine consistently demonstrated higher neurodevelopmental scores than those on standard dosing. Cognitive and language improvements were especially notable.

Discussion: Findings from this randomized controlled follow-up study highlight the significant neurodevelopmental advantages associated with early high-dose levothyroxine therapy in congenital hypothyroidism. The observed improvements across cognitive, language, and motor domains support the hypothesis that prompt hormonal optimization during the critical neonatal period enhances long-term neurological integrity. These results align with emerging evidence that even slight delays or suboptimal dosing in early treatment can lead to measurable deficits in cerebral maturation.¹³⁻¹⁵

The greater cognitive and linguistic gains detected at both two years and five years indicate that early hormonal sufficiency exerts sustained effects on higher cortical functions. Language pathways, which depend heavily on adequate myelination and synaptic organization, appeared especially responsive to the more rapid biochemical correction achieved in the early-high-dose cohort. The strong correlation between earlier thyroid normalization and higher cognitive performance further reinforces the biological plausibility of these findings.¹⁶⁻¹⁸

Motor improvements, although less pronounced, still demonstrated benefits of intensified early therapy. Motor development is influenced by both central and peripheral mechanisms, and the observed gains suggest that early hormonal adequacy supports integrated neuromuscular maturation. Although overtreatment remains a potential concern, serial monitoring throughout follow-up showed no increase in adverse events, indicating that carefully supervised high initial dosing can be safely administered.¹⁹⁻²⁰

A crucial implication of these findings lies in the timing of treatment. Initiation within the first week of life, accompanied by adequate dosing, may represent the optimal window for intervention. This is especially pertinent in low-resource contexts where delays in diagnostic confirmation or treatment commencement may remain common. By demonstrating clear long-term benefits, the study underscores the importance of strengthening screening programs and promoting early neonatal endocrine management.

The randomized design and long-term follow-up strengthen the validity of the study, though limitations warrant consideration. Socioeconomic and environmental factors, which inherently influence neurodevelopment, were accounted for but may still exert residual effects. Additionally,

the follow-up period ends at five years; ongoing monitoring could reveal further divergence or stabilization of developmental trajectories. Despite these constraints, the evidence strongly supports early hormonal optimization as a cornerstone of congenital hypothyroidism management.

Conclusion: Early high-dose levothyroxine therapy initiated within the first week of life significantly improves long-term neurodevelopmental outcomes in children with congenital hypothyroidism. Cognitive and language benefits were the most pronounced, highlighting the critical role of timely hormonal correction during early brain development. Strengthening newborn screening and ensuring rapid initiation of optimized therapy can reduce the neurodevelopmental burden associated with this condition.

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