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Frequency and Characteristics of Hypothyroidism in Neonatal Intensive Care Unit Patients in a Tertiary Care Hospital

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Author`s Contribution

[1,2]Substantial contributions to the conception or design of the work; or the acquisition, [3]Final approval of the study to be published, [4]Active participation in active methodology, [5,6]Drafting the work or revising it critically for important intellectual content, analysis, or interpretation of data for the work,

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ABSTRACT

Objective: To Investigate frequency, clinical and laboratory profiles of hypothyroidism in neonates admitted to the Neonatal Intensive Care Unit (NICU) in a tertiary care hospital.

Methodology: This Prospective, cross-sectional study Neonatology Department, Fatima Memorial Hospital, Lahore, from July 2024 to December 2024. A total of 200 neonates admitted in NICU were included using consecutive non-random sampling. Thyroid function was assessed through serum free T4 and TSH levels, with hypothyroidism diagnosed based on low free T4 or elevated TSH levels and clinical symptoms. Data were analyzed using SPSS 25.0, with statistical significance set at $p < 0.05$.

Results: Among 200 neonates, 23 (11.5%) were diagnosed with congenital hypothyroidism (CH), while 33 (16.5%) exhibited subclinical hypothyroidism. Low free T4 levels were observed in 21 (10.5%) neonates, and high TSH levels in 36 (18%). Feeding intolerance was the most common clinical symptom noted in 52.5% of cases. Significant maternal factors associated with CH included gestational illness ($p = 0.008$), antenatal steroid use ($p = 0.003$), and multiple gestations ($p = 0.027$). Predominant neonatal risk factors were preterm birth ($p < 0.001$), cesarean delivery ($p = 0.016$), and intrauterine growth restriction (IUGR) ($p = 0.044$). The prevalence of hypothyroidism was higher in preterm ($p <0.001$) and low-birth-weight neonates ($p = 0.191$), highlighting the vulnerability of this subgroup.

Conclusion: Congenital hypothyroidism is prevalent in NICU patients, particularly those born preterm or with low birth weight. Maternal and neonatal factors significantly influence the risk.

Keywords: Congenital hypothyroidism, Hypothyroxinemia, Maternal risk factors, Neonates, Neonatal screening, NICU, Preterm infants, Thyroid function tests, Thyroid dysfunction.

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Introduction

Congenital hypothyroidism (CH) is one of the most common endocrine disorders in children.[1] It can be easily prevented through early diagnosis and prompt treatment.[2] However, if left undiagnosed or untreated, it can result in significant delays in child's physical growth and mental development, and puberty.[3] It is defined as a deficiency of thyroid hormones or impaired thyroid function present at birth.[4] CH is classified into two types: permanent CH and transient CH. Permanent CH is characterized by persistent thyroid hormone deficiency, requiring lifelong treatment. In contrast, transient CH, involves a temporary deficiency in thyroid function, with recovery typically occurring within the first few months or years after birth.[2]

During the antenatal period, the fetus depends on maternal thyroid hormones, as the fetal thyroid gland

begins to function around 10–12 weeks of gestation but does not fully mature until the second trimester.[5] Placental transfer of maternal thyroxine (T4) plays a crucial role in fetal neurodevelopment during the first trimester and early second trimester, especially before the fetal thyroid gland becomes functional. At birth, the neonate undergoes a surge in thyroid-stimulating hormone (TSH), which stimulates the thyroid gland to produce T4 and triiodothyronine (T3). However, preterm neonates often experience delayed or insufficient TSH surge, leading to transient hypothyroxinemia.[6]

Maternal thyroid hormones provide critical support until the fetal thyroid axis is functional, typically up to 18–20 weeks of gestation.[7] Maternal thyroid hormones if deficient during this period can result in impaired fetal brain development. Cretinism, a severe form of untreated congenital hypothyroidism, appear later in infancy, usually after 3–6 months, and its clinical manifestations include poor feeding, lethargy, coarse facial features, macroglossia, and developmental delay.[5]

Hypothyroxinemia in neonates can result from various factors, including low thyroid-binding globulin (TBG) during the first 2 weeks of life, decreased T4 binding affinity to TBG, limited thyroid gland reserve, or an obtunded neonatal TSH surge. Other contributing factors include minimal T4 to T3 conversion, immaturity of the hypothalamic-pituitary-thyroid (HPT) axis, and intrauterine growth restriction (IUGR). Certain medications, such as dopamine, dexamethasone, and aminophylline. In addition, common conditions like respiratory distress syndrome (RDS), sepsis, necrotizing enterocolitis, and extra-uterine growth restriction can also impair thyroid function. Moreover, causes include non-thyroidal illness, iodine deficiency, withdrawal of maternal-placental T4 transfer, perinatal asphyxia, limited thyroglobulin iodine stores.[8] These factors collectively highlight the complexity and multifactorial nature of hypothyroxinemia in neonates.

Sick euthyroid syndrome, also known as non-thyroidal illness syndrome (NTIS), is a state of abnormal thyroid function observed in critically ill neonates without underlying thyroid gland dysfunction. It is characterized by low levels of T3, with normal or low T4 and TSH, often as an adaptive response to illness rather than true hypothyroidism. This transient thyroid dysfunction is commonly seen in preterm or critically ill neonates admitted to the NICU, and its severity correlates with the degree of illness rather than primary thyroid dysfunction[9]. Hypothyroxinemia of prematurity refers to a condition in which preterm neonates exhibit low T4 levels with normal or slightly low TSH. It occurs due to immaturity of the HPT axis, inadequate TSH surge at birth, and limited thyroid hormone stores. Other contributing factors include iodine deficiency, perinatal asphyxia, and systemic illness. While typically transient, severe cases may impact neurodevelopment, warranting close monitoring and consideration for treatment in extremely preterm infants[10]. The prevalence of CH is approximately 1 in 400 in preterm or low-birth-weight neonates compared to 1 in 4,000 in term infants.[4]

The overall incidence of CH ranges from 1 in 3,000 to 1 in 4,000 live births, with variation worldwide among different ethnicity.[11] The incidence is notably higher in Hispanic (1 in 1600) and Asian (1 in 2380) infants while it is lower in Black infants (1:11,000).[12] CH is also more common in females, with a female-to-male ratio of approximately 1.5 or 2:1.[12] Additionally, the incidence is higher in twin and multiple births, infants born to older mothers, and preterm infants.[12,13] In Pakistan, the exact incidence and prevalence of CH are not well established and national data is also lacking in prevalence of CH in sick neonates. However, a study conducted at Aga Khan University Pakistan regarding neonatal screening for CH reported that the incidence of CH is more than four times higher compared to that in Western countries.[14] in healthy neonates and national data is lacking in prevalence of CH in sick neonates. International studies have reported a high prevalence of CH in term neonates admitted in NICU. For instance, a study done in India shows hypothyroxinemia in 10.2%[9] in neonates admitted in NICU while another study from Iran shows 40 folds higher TSH in critically ill neonates as compared to healthy neonates.[15]

In Pakistan, the true magnitude of CH remains unknown as newborn screening is not mandatory for all neonates, leading to many undiagnosed and untreated cases. This lack of early detection can result in irreversible health damage and significant psychological distress for families. Prompt diagnosis and treatment of thyroid dysfunction in neonates are crucial, underscoring the need for clinicians to be fully aware of CH and its implications.[16] However, no robust local data found on prevalence of congenital hypothyroidism in sick neonates in NICUs. We suspect the frequency of hypothyroidism is more in sick neonates especially preterm babies. Recognizing the importance of this condition, this study aimed to investigate the frequency of hypothyroidism and assess its clinical and laboratory profiles in NICU

patients at a tertiary care hospital. Given the higher frequency of thyroid dysfunction in sick and preterm neonates, the findings are expected to contribute valuable insights into improving neonatal screening and management programs.

Methodology

This was a prospective cross-sectional study conducted in the Neonatal Intensive Care Unit (NICU), Department of Neonatology, Fatima Memorial Hospital, Lahore, from July 2024 to December 2024. The sample size of 200 neonates was calculated using the WHO sample size calculator (version 1.1), based on an expected prevalence of hypothyroxinemia of 8.2% in NICU neonates[17], with a 95% confidence level and 4% precision.

All neonates admitted to the NICU up to 44 weeks of postmenstrual age (PMA) who were routinely screened for hypothyroidism were included. The inclusion criteria ensured that only neonates requiring specialized care were studied, including syndromic babies and those with congenital anomalies.

Neonates admitted to the NICU who were not tested for hypothyroidism were excluded. This included those who did not undergo testing due to early discharge or parental refusal.

Ethical approval was obtained from the hospital's ethical review committee (IRB no. FMH-20/03/2024-IRB-1373). Eligible patients were enrolled after obtaining parental or guardian consent. A consecutive non-random sampling technique was used. All relevant maternal and neonatal data were collected using a structured proforma.

Blood samples were obtained by heel prick. Serum free T4 and TSH were measured using the Abbott Architect i1000SR analyzer with the chemiluminescence method. Results were interpreted against the reference values provided in Table 10.6 of *The Harriet Lane Handbook, 23rd Edition.*[18]

Congenital hypothyroidism (CH) was diagnosed based on the following criteria: high TSH with low free T4, both low TSH and free T4, or normal TSH with low free T4.[19] It was also considered when high TSH with normal free T4 was accompanied by at least one clinical feature of hypothyroidism (e.g., temperature instability, feed intolerance, apnea, extubation failure ≥2 times, prolonged jaundice, constipation, myxedema, or goiter). Asymptomatic neonates with abnormal biochemical profiles were labeled as having "subclinical hypothyroidism," and repeat screening was advised after a minimum interval of three weeks.[20,21]

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0. Descriptive statistics were presented as means with standard deviations for continuous variables, and frequencies with percentages for categorical variables. Point estimation was used to calculate the prevalence of hypothyroidism in NICU neonates. Regression analysis was performed to identify risk factors for early detection of hypothyroidism. A p-value <0.05 was considered statistically significant.

Results

Out of 200 neonates, 145 (72.5%) neonates were born in the hospital, while the remaining 55 (27.5%) neonates were born outside the hospital. The mean gestational age was 35.68 ± 3.53 weeks. The mean birth weight was recorded 2.24 ± 0.77 kg. The mean APGAR score was 7.46 ± 1.14 at 1min and 8.52 ± 0.98 at 5 min. Thyroid screening was performed at mean age of 7.43 ± 4.71 days.

Out of 200, 105 (52.5%) neonates exhibited at least 1 sign or symptom of hypothyroidism. Among these, feeding intolerance was the most common symptom observed. Prolonged jaundice, Myxedema and Goiter was not found in any neonate. The frequency of each sign and symptom of hypothyroidism is illustrated in figure 1.

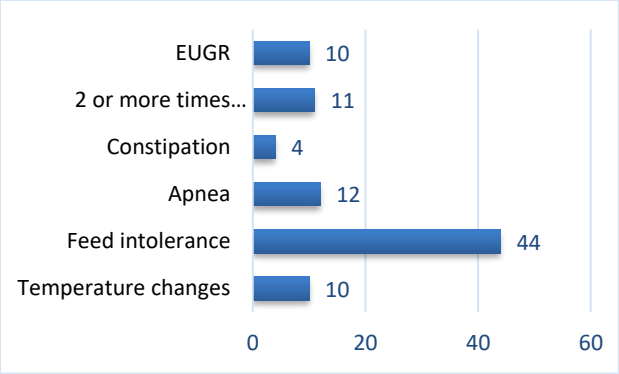

Figure 1. Bar chart of frequency of signs and symptoms of hypothyroidism.

Sepsis was the most common post-natal factor observed in 74 (37%) neonates, followed pneumonia 72 (36%), Patent ductus arteriosus (PDA) 56 (28%) and respiratory distress syndrome (RDS) 44 (22%) was the prominent post-natal factors observed in the study. The detail frequency of all post-natal factors is mentioned in figure 2.

No mother of the selected neonates in the study, was found to use antithyroid drugs, not having family history of thyroid disease and no case of maternal antibodies was found.

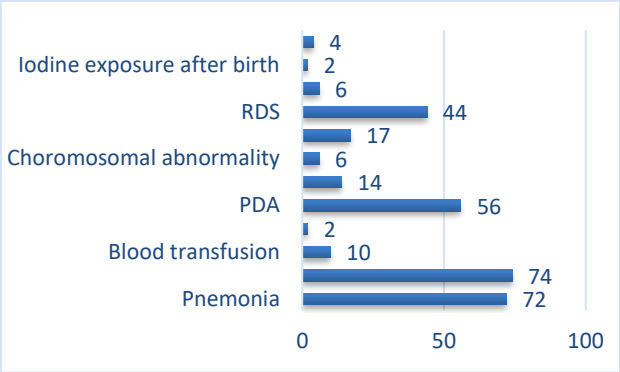

Figure 2. Bar chart of frequency of post-natal factors.

The neonates were admitted in the NICU because of different reasons. Out of total 200 neonates, 59(29.5%) admitted due to prematurity, 25(12.5%) with respiratory distress syndrome (RDS), 43(21.5%) because of neonatal sepsis, 27(13.5%) with neonatal jaundice, 23(11.5) due to low birth weight and 23(11.5%) were admitted due to any congenital anomalies.

Free T4 was found 'Low' in 21 (10.5%) neonates whereas TSH was found 'High' in 36 (18%) neonates, and 'Low' in 11 (5.5%) neonates. Congenital hypothyroidism was diagnosed in 23 (11.5%) cases, whereas repeat test was suggested in 33 (16.5%) cases labeled as 'Sub-clinical'. The result shows that in neonates who were already not stable and admitted in NICU, the prevalence of CH in neonates admitted in NICU was at least 7.5%. The stratification of the results showed that the prevalence of congenital hypothyroidism is associated with some maternal factors i.e. gestational illness, used of antenatal steroids and multiple gestation with p value 0.008, 0.003 and 0.027, respectively. Preterm birth, mode of delivery and intrauterine growth restriction (IUGR) are significant neonatal factors associated with congenital hypothyroidism with p value <0.001, 0.016 and 0.044, respectively. The detail of

Table I: Maternal and Natal characteristics relationship of occurrence of hypothyroidism with maternal and neonatal characteristics. (n=200)

Factors		N(%)	Hypothyroidism (n=200)			p value
			Congenital	Sub-clinical	Normal	
Gestational Illness (Pregnancy induced hypertension, Gestational diabetes mellitus, PROM, Obstetric cholestasis)	Yes	98(49%)	13 (43.5)	8 (24.2)	77 (53.5)	0.008
	No	102(51%)	10 (56.5)	25 (75.8)	67 (46.5)	
Septic risk factors	Yes	24(12%)	3 (13)	1 (3)	20 (13.9)	0.139
	No	176(88%)	20 (87)	32 (97)	124 (86.1)	
Antenatal Steroid	Yes	49(24.5%)	9 (39.1)	1 (3)	39 (27.1)	0.003
	No	151(75.5%)	14 (60.9)	32 (97)	105 (72.9)	
Thyroxine intake	Yes	4(2%)	0	1 (3)	3 (2.1)	0.580
	No	196(98%)	23 (100)	32 (97)	141 (97.9)	
Weight gain during pregnancy	Yes	38(19%)	8 (34.8)	5 (15.2)	25 (17.4)	0.152
	No	162(81%)	15 (65.2)	28 (84.8)	119 (82.6)	
Multiple gestations	Yes	26(13%)	0	6 (18.2)	20 (13.9)	0.027
	No	174(87%)	23 (100)	27 (81.8)	124 (86.1)	
Preterm	Yes	95(47.5%)	19 (82.6)	22 (66.7)	54 (37.5)	<0.001
	No	105(52.5%)	4 (17.4)	11 (33.3)	90 (62.5)	
Low Birth weight	Yes	120(60%)	17 (73.9)	22 (66.7)	81 (56.3)	0.191
	No	80(40%)	6 (26.1)	11 (33.3)	63 (43.8)	
SGA	Yes	28 (14%)	5 (21.7%)	3 (9.1%)	20 (13.9%)	0.565
	No	172 (86%)	18 (78.3%)	30 (90.9%)	124(86.1%)	
AAG	Yes	166 (83%)	18 (78.3%)	29 (87.9%)	119(82.6%)	0.876
	No	34 (17%)	5 (21.7%)	4 (12.1%)	25 (17.4%)	
LGA	Yes	6 (3%)	0	1 (3%)	5 (3.5%)	0.408
	No	194 (97%)	23 (100%)	32 (97%)	139(96.5%)	
Mode of delivery	SVD	42(21%)	4 (17.4)	6 (18.2)	32 (22.2)	0.016
	Em-LSCS	130(65%)	15 (15.2)	27 (81.8)	88 (61.1)	
	El-LSCS	28(14%)	4 (17.4)	0	24 (16.7)	
Gender	Male	113(56.5%)	14 (60.9)	16 (48.5)	83 (57.6)	0.572
	Female	87(43.5%)	9 (39.1)	17 (51.5)	61 (42.4)	
Intubation	Yes	18(9%)	1 (4.3)	2 (6.1)	15 (10.4)	0.481
	No	182(91%)	22 (95.7)	31 (93.9)	129 (89.6)	
Anomalies like micropenis/undescended testis/umbilical hernia/wide fontanelle/cataracts	Yes	6(3%)	1 (4.3)	0	5 (3.5)	0.326
	No	194(97%)	22 (95.7)	33 (100)	139 (96.5)	
IUGR	Yes	46(23%)	10 (43.5)	6 (18.2)	30 (20.8)	0.044
	No	154(77%)	13 (56.5)	27 (81.8)	114 (79.2)	

maternal history and natal events and the cross-tabulation results are mentioned in table I.

The analysis of the results also showed that the congenital hypothyroidism is associated with some post-natal factors i.e. PPHN, PDA and sepsis with p value 0.026, 0.002 and 0.014 respectively. The details of association of post-natal with congenital hypothyroidism are mentioned in Table II.

Discussion

Our study's findings on the prevalence of CH contribute to the growing body of literature on this condition, both within Pakistan and globally. The observed frequency of CH in our cohort aligns with, yet also presents distinctions from, various local and international studies. The overall prevalence of CH in our study is 11.5%, including 16.5% of cases categorized as subclinical hypothyroidism, these findings significantly exceed the global incidence of CH in the general neonatal population, typically reported as 1 in 3,000 to 1 in 4,000 live births.[22]

In Pakistan, the reported incidence rates of CH vary across different studies. For instance, a study conducted by Khokhar AR, et al[23] in district Dera Ghazi Khan, reported a notably high frequency of CH, with 8% of neonates being diagnosed with the condition. Similarly, in another local study, Khalil R et al[17] also demonstrated a high frequency of CH in neonates. Both of the studies have comparable results with our study. But on the other hand, in many studies the researchers reported low prevalence of CH, like a study of Batool B et al[24] reported a CH prevalence of 2% among screened neonates and another study from a tertiary care hospital in Lahore found a CH incidence of approximately 0.4%.[25] Comparisons with other studies reveal variations that may be attributed to differences in population characteristics, screening protocols, and study designs.

On a global scale, a meta-analysis encompassing data from 1969 to 2020 estimated the pooled global prevalence of CH to be 4.25 per 10,000 neonates. The study highlighted regional variations, with the Eastern Mediterranean region exhibiting the highest prevalence at 7.91 per 10,000 neonates. Additionally, the analysis observed a 52% increase in global CH prevalence in the period from 2011 to 2020 compared to 1969 to 1980.[26]

The maternal and neonatal risk factors identified in this study further elucidate the complex interplay of conditions contributing to CH. Significant maternal factors, including antenatal steroid use and multiple gestations, align with observations in recent literature suggesting that maternal stress and perinatal interventions may modulate neonatal thyroid function.[27,28] Neonatal factors such as preterm birth, intrauterine growth restriction (IUGR), and delivery via cesarean section also emerged as significant predictors of CH, corroborating

Table II: Relationship of postnatal factors with congenital hypothyroidism. (n=200)

Post-natal factors	categories	Hypothyroidism categories			p value
		Congenital hypothyroidism n (%)	Sub-clinical n (%)	Normal n (%)	
Hypoglycemia	No	23 (100)	31 (93.9)	142 (98.6)	0.218
	Yes	0	2 (6.1)	2 (1.4)	
Iodine exposure	No	23 (100)	33 (100)	142 (98.6)	0.516
	Yes	0	0	2 (1.4)	
AKI	No	23 (100)	32 (97)	139 (96.5)	0.471
	Yes	0	1 (3)	5 (3.5)	
RDS	No	14 (60.9)	26 (78.8)	116 (80.6)	0.106
	Yes	9 (39.1)	7 (21.2)	28 (19.4)	
NEC	No	20 (87)	31 (93.9)	132 (91.7)	0.635
	Yes	3 (13)	2 (6.1)	12 (8.3)	
DS	No	23 (100)	31 (93.9)	140 (97.2)	0.823
	Yes	0	2 (6.1)	4 (2.8)	
PPHN	No	23 (100)	33 (100)	130 (90.3)	0.026
	Yes	0	0	14 (9.7)	
PDA	No	15 (65.2)	16 (48.5)	113 (78.5)	0.002
	Yes	8 (34.8)	17 (51.5)	31 (21.5)	
HIE	No	23 (100)	33 (100)	142 (98.6)	0.413
	Yes	0	0	2 (1.4)	
Blood Transfusion	No	20 (87)	33 (100)	137 (95.1)	0.333
	Yes	3 (13)	0	7 (4.9)	
Sepsis	No	12 (52.2)	28 (84.8)	86 (59.7)	0.014
	Yes	11 (47.8)	5 (15.2)	58 (40.3)	
Pneumonia	No	12 (52.2)	22 (66.7)	94 (65.3)	0.449
	Yes	11 (47.8)	11 (33.3)	50 (34.7)	

the findings of studies that link prematurity with delayed TSH surges and transient hypothyroxinemia.[29]

The clinical presentation of CH in this study was predominantly subtle, with feeding intolerance being the most frequent symptom, while classic features like prolonged jaundice, myxedema and goiter were notably absent. This aligns with the growing recognition that the presentation of CH in neonates is often nonspecific, particularly in preterm infants, necessitating reliance on systematic screening for early detectionl[30] Laboratory findings further emphasized the complexity of neonatal thyroid dysfunction, with 10.5% of neonates showing low free T4 levels and 18% exhibiting elevated TSH levels. These results underscore the importance of repeated thyroid function tests to distinguish transient hypothyroidism from permanent CH, as transient conditions may resolve spontaneously, while undiagnosed permanent cases can lead to significant neurodevelopmental delays.[29,31]

The higher prevalence of CH and subclinical hypothyroidism identified in this study compared to global and regional reports underscores the need for routine thyroid function screening in NICU settings. The findings advocate for the early identification and timely management of thyroid dysfunction, particularly in high-risk neonates, to prevent adverse developmental outcomes. Given the study's single-center design and limited sample size, future multicenter research with larger cohorts and extended follow-up is essential to validate these findings and refine neonatal thyroid screening guidelines.

Conclusion

This study highlights a notably high prevalence of CH among neonates admitted to the NICU. The findings emphasize the critical need for routine thyroid function screening in this high-risk population. Maternal and perinatal factors, including antenatal steroid use and cesarean delivery, were identified as key contributors to the increased risk of CH, underscoring the importance of comprehensive maternal and neonatal care. Early diagnosis and timely intervention are crucial to preventing long-term neurodevelopmental impairments. More studies are needed to build up on evidence obtained from our study.

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