

Thyroid Function in Healthy Preterm Infants at the NICU of Assiut University Children's Hospital: An Observational Study

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Abstract:

Introduction: Thyroid dysfunction is a common issue in preterm infants; physiological hypothyroxinemia is the most common thyroid function disorder in premature infants, followed by hypothyroidism from non-thyroidal causes. A number of conditions, including malnutrition, hypoxemia, acidosis, infections, hypoglycemia, and hypocalcemia, can slow the conversion of peripheral T4 to T3 in preterm.

Objectives: Assess thyroid function in healthy preterm neonates on days 3–5 and 14.

Patients and Methods: This observational study was done at the Neonatal Intensive Care Unit at Assiut University Children's Hospital, and included all preterm infants at the time of research, but those with any medical problems, fatal congenital malformations, or Children whose parents declined to take part in this research were not included. Anthropometric measurements, personal information, and those lab tests were recorded.

Results: On days 3-5, three patients (6%) had hypothyroxinemia of prematurity, and four cases (8%) had hyperthyrotropinemia. On day 14, two cases (4%) and three cases (6%) had hypothyroxinemia of preterm and Hyperthyrotropinemia, respectively. Although there were more thyroid abnormalities overall on day 3 than on day 14, the difference was not statistically significant ($p>0.05$). Furthermore, a noteworthy correlation was observed between thyroid function, gestational age, and birth weight.

Conclusion: Both birth weight and gestational age have an impact on thyroid dysfunction in preterm newborns.

Keywords: Preterm; Thyroid function; Hypothyroidism, Hypothyroxinemia.

Introduction:

The thyroid hormone is the foundation of a complex system crucial to a child's growth and development, particularly the development of the neurological system and brain. Thus, even slight perturbations to this system have the potential to result in permanent damage [1].

Preterm infants frequently experience thyroid dysfunction [2], with physiological hypothyroxinemia being the most common thyroid function disorder, followed by hypothyroidism from non-thyroidal causes. Transient secondary/tertiary hypothyroidism, transient primary hypothyroidism, and

permanent primary hypothyroidism are rare conditions that can also occur [3].

A number of conditions, including hypoxemia, acidosis, infections, hypoglycemia, hypocalcemia, and malnourishment, can prevent the conversion of peripheral T4 to T3 in preterm [4].

Aim of work: To evaluate thyroid function in healthy preterm infants on days 3-5 and day 14.

Patients and Methods:

This observational study was carried out at the Neonatal Intensive Care Unit of Assiut University Children's Hospital over a year, from December 1, 2021, to November 30, 2022. Among the participants were 50

healthy preterm infants who came for their routine postnatal checkup at the neonatal unit's outpatient clinic and did not report any problems. Patients who did not finish the study period, cases with any medical issues, infants whose parents refused to participate, and extremely preterms (less than 28 weeks of gestational age) were also excluded.

All included infants were subjected to the following preliminary evaluation:

1. Recording the following information from the patient's medical history: name, gestational age, sex, number of pregnancies, pregnancy complications (such as gestational diabetes, PRoM, preeclampsia, eclampsia, placenta previa, etc.), delivery complications, and delivery mode.
2. A comprehensive clinical examination includes a systemic, anthropometric, and general examination.
3. Laboratory testing: Using a chemiluminescence immunoassay (CLIA), peripheral venous blood samples were tested for TSH, free T4, and free T3 on days 3-5 and

Operational definitions:-

- Congenital hypothyroidism is defined as: TSH level ≥ 20 mIU/L, or >10 mIU/L

together with a low level of free T4 <0.8 ng/dl [5].

- Hyperthyrotropinemia (HT) is defined as a concomitant increase in the TSH level >10 mIU/L and a normal free thyroxine (T4) level [6].
- Hypothyroxinemia of prematurity HTOP is defined as decreased free T4 <0.8 ng/dl with normal TSH level in preterm infants [6].

Statistical Analysis:

- Data were collected from the patients' clinical interpretation at presentation and medical records.
- Computer software: SPSS Program, version 20, was used.

Ethical Considerations:

- Approval from the Ethics of Scientific Research Committee, Faculty of Medicine, Assiut University was obtained.
- Verbal and written consents were obtained from all the patients' caregivers.
- The privacy and confidentiality of all information obtained were observed without intervention in the prescribed treatment.

IRB NUM: 17101383

Result

Table (1): Baseline characteristics in healthy preterm infants (n=50)

Baseline characteristics		No.	%
Sex	Male	21	42.0%
	Female	29	58.0%
Type of delivery	Vaginal delivery	7	14.0%
	C.S	43	86.0%
Multiple pregnancies		9	18%
Pregnancy complications	No	30	60.0%
	Eclampsia	0	0.0%
	GDM	3	6.0%
	Placenta previa	4	8.0%
	Preeclampsia	5	10.0%
	PROM	8	16.0%
Gestational age (weeks)	Mean $\pm$ SD	33.18 $\pm$ 1.16	
	Median (IQR)	33.0 (32.0-34.0)	
	Range	31.0- 36.0	
Birth weight (g)	Mean $\pm$ SD	1967.0 $\pm$ 431.64	
	Range	1300- 2900	

Table (2): Thyroid abnormalities detected at day 3-5 & day 14 in healthy preterm infants

Thyroid abnormalities		No.	%
At day 3-5	Total number of abnormal thyroid functions	7	14.0%
	- Congenital hypothyroidism	0	0.0%
	- Hypothyroxinemia of prematurity	3	6.0%
	- Hyperthyrotropinemia	4	8.0%
At day 14	Total number of abnormal thyroid functions	5	10.0%
	- Congenital hypothyroidism	0	0.0%
	- Hypothyroxinemia of prematurity	2	4.0%
	- Hyperthyrotropinemia	3	6.0%
P-value between day 3-5 and day 14*		0.805 (NS)	

Three cases (6%) of hypothyroxinemia of prematurity and four cases (8%) of hyperthyrotropinemia were observed at days 3-5. Two cases (4%) of hypothyroxinemia of prematurity and three cases (6%) of

hyperthyrotropinemia were observed at day 14.

Although there were more thyroid abnormalities overall on day 3 than on day 14, the difference was insignificant in either group ($p>0.05$).

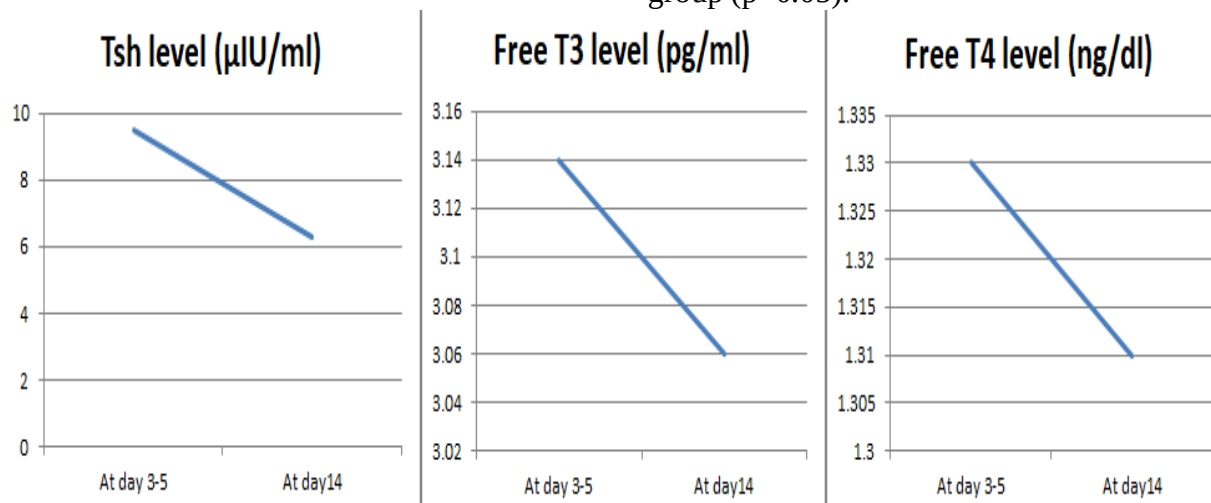


Fig 1: comparison between day 3-5 and day 14 as regards TSH, free T3, and Free T4 in healthy preterm

There was a statistically significant decrease in TSH level at day 14 compared to its level at day 3 ($p<0.001$). Free T3 and T4 levels tended to decrease at day 14 compared

to their levels at day 3, but this decrease did not reach a significant level.

Table (3): Correlations between TSH, free T3, and Free T4 levels & different parameters in healthy preterm

	TSH level		Free T3 level		Free T4 level	
	r	p- value	r	p- value	r	p- value
Gestational age	-.408-	<0.001	.470	.001	.499	<0.001
Sex	-.010-	.946	-.213-	.137	-.013-	.930
Birth Weight	-.599-	<0.001	.475	<0.001	.654	<0.001
Head Circumference	-.138-	.340	.068	.638	.153	.289
Length	-.239-	.094	.193	.178	.076	.599
Type Of Delivery	.175	.224	-.062-	.668	-.047-	.744

$p \leq 0.05$ is significant, $p \leq 0.01$ is highly significant, r : Spearman correlation

There was a significant negative correlation between TSH level and gestational age and birth weight, with ($r = -0.408$, $p < 0.001$) and ($r = -0.599$, $p < 0.001$), respectively. But there was a significant positive correlation between free T3 level with gestational age and birth weight ($r =$

0.470 , $p = 0.001$) and ($r = 0.475$, $p < 0.001$) respectively. And also significant positive correlation between free T4 level with gestational age and birth weight ($r = 0.499$, $p < 0.001$) and ($r = 0.645$, $p < 0.001$) respectively.

Table (4): Relation between gestational age and thyroid function levels.

	Kruskal-Wallis test							
	28-32 weeks (N=11)			32-36 weeks (N=86)				
	Median	Range		Median	Range		Test value (z_{MWU})	P-value
TSH level (μ IU/ml)	11.80	1.10	15.4	7.50	0.50	16.20	7.174	0.029 (S)
Free T3 level (pg/ml)	1.80	1.20	2.70	2.70	1.60	4.60	23.38	<0.001 (HS)
Free T4 level (ng/dl)	0.90	0.50	1.10	1.25	0.50	1.80	16.706	<0.001 (HS)

$P \leq 0.05$ is statistically significant, $p \leq 0.01$ is highly significant, SD: standard deviation.

There was a statistically significant relationship between gestational age and TSH level, free T3 level, and free T4 level. TSH level was significantly higher at GA 28-32 weeks than at 32-36 weeks. Free T3 level and free T4 level significantly increased at GA 32-36 weeks compared to their levels at 28-32 weeks.

Discussion:

Compared to term babies, preterm babies have lower serum thyroid hormone levels. This is because preterm babies have a lesser postnatal pituitary-thyroid function, a lesser postnatal thyroid-stimulating hormone (TSH) surge after birth, and a lower maternal contribution [7].

As might be observed with thyroid hypoplasia, an ectopic gland, or moderate dyshormonogenesis, the absence of symptoms and signs of hypothyroidism is most likely caused by transplacental transfer of some maternal thyroid hormone in addition to some residual neonatal thyroid function [8].

The results of the study on thyroid function in the enrolled cases revealed that, on the third and fifth day of life, the healthy preterm showed that 7 cases (14%) had

abnormal thyroid function, manifested as hyperthyrotropinemia in four of them (8%) and hypothyroxinemia of prematurity in 3 cases (6%).

After 14 days of life, five healthy preterm patients (10%) had abnormal thyroid function, which manifested as 2 cases (4%) of hypothyroxinemia of prematurity and 3 cases (6%) of hyperthyrotropinemia.

Kim et al. sought evidence for thyroid hormone supplementation by assessing the prevalence of thyroid dysfunctions and the impact of low T4 levels on neonatal morbidity. It was shown that 17 out of 32 (53.1%) babies had thyroid dysfunction: 12 babies (37%) had hypothyroxinemia, four babies (12%) had hypothyroidism, and one baby (3%) had hyperthyrotropinemia [9].

Chen et al. sought to determine the frequency of thyroid dysfunction, examine trends in thyroid function tests (TFT) in preterm newborns, and pinpoint the variables influencing thyroid function. According to their findings, 50.3% of people have thyroid dysfunction overall. Eleven babies, or 5.8%, exhibited delayed TSH rise [10].

Consistent with our findings, Chung et al. discovered that of 105 preterm newborns, 31 cases (28%) had hypothyroxinemia of prematurity, and 13 cases (12%) had hypothyroidism diagnoses.

Thyroid function monitoring in preterm infants is required to identify the specific cases of thyroid abnormalities, as our study revealed that the total number of thyroid abnormalities detected at day 3 was higher than the total number of abnormalities detected at day 14. However, this difference did not reach a significant value ($p>0.05$). In line with our findings, Zdraveska et al. stated that many screening programs advise a second screening test for preterm newborns, low birth weight babies, neonates from multiple births, and sick newborns admitted to the neonatal intensive care unit at 2 or 4 weeks of life due to the possibility of both false-positive and false-negative screening results [11].

Regarding the relationship between thyroid function and a number of parameters in healthy preterm infants, the TSH level and birth weight had a significant negative association ($r=-0.599$, $p<0.001$) and gestational age ($r=-0.408$, $p<0.001$), respectively. However, there was a strong positive association ($r=0.475$, $p<0.001$) and a substantial positive correlation ($r=0.470$, $p=0.001$) between the free T3 level and the birth weight and gestational age. Additionally, there is a strong positive connection ($r = 0.499$, $p<0.001$) between the free T4 level and the birth weight and gestational age ($r = 0.645$, $p<0.001$), respectively.

Williams FL et al. reported that FT4 levels on day 7 were positively associated with Gestation at days 7, 14, and 28, correspondingly, (1.85), (1.26), and (0.77 pmol/liter each week), which supports our results [12].

Transient hypothyroxinemia of prematurity was found to be strongly correlated with lower birth weight and GA by Chen et al. and to have significant relationships with gestational week and birth weight by Korkmaz et al [13].

Gestational age was correlated statistically significantly with TSH, free T3, and free T4 levels. Compared to its level at 32–36 weeks, the TSH level was much higher at GA 28–32 weeks. In contrast to its level at 28–32 weeks, the freeT3 and freeT4 levels at GA 32–36 weeks were considerably higher.

Chung et al. similarly observed considerably decreased FT4 levels in newborns born before 28 weeks of Gestation, consistent with our findings [14]. They observed that throughout the first postnatal week, low FT4 levels persisted, but over the first two months, these levels returned to normal for term newborns. Klosinska et al. also discovered that the free T4 levels in preterm neonates peak between PMA=26–27 weeks and return to normal between PMA=38–40 weeks (76, 77) [15].

Additionally, Celmente et al. reported that healthy PTN 27-29 weeks had lower TSH peak at 1 hour and lower free T4, T3, and T4 values during the first 2 months than healthy PTN 30-35 weeks (PTN30-35w). They aimed to examine thyroid function in preterm neonates 28 (PTN) 27-29 weeks of gestational age [16].

Conclusion:

- During the first two weeks of life, preterm infants experience substantial thyroid dysfunction more often at ages 3-5 days than at 14 days.
- Birth weight and gestational age have an impact on thyroid function in preterm infants; this effect is particularly prevalent in preterm babies between 28 and 32 weeks.
- The most prevalent form of hyperthyrotropinemia is thyroid dysfunction.

Recommendations:

- Longer follow-up studies are advised to determine the impact of thyroid dysfunction in preterm infants on their neurocognitive function.
- Thyroid function tests should be closely monitored in preterm infants.

A larger study is advised to detect the relationship between thyroid function in sick

preterm infants and the correlation between healthy and sick groups.

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