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Detect delayed thyroid stimulating hormone elevation in preterm neonates at age of one month

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Abstract
Background: The promotion of early foetal tissue growth and development is facilitated by thyroid hormones. This study sought to examine if instances of the existing screening programme would miss cases of congenital hypothyroidism as well as to identify delayed thyroid stimulating hormone (TSH) increase with gestational age in preterm neonates (33 weeks) at age one month.
Methods: In this prospective study, 50 preterm neonates with gestational ages between 33 weeks and less than ≤1.8 kg were included. They were split into two equal groups: Group 1 contained low birth weight (LBW) infants, defined as those weighing less than 1.8 kg at delivery (1.5:1.8 kg). Baby born with a very low birth weight (VLBW) of less than 1.5 kg is in group 2. During the first week after birth and again at one month, free thyroxine hormone (FT4), free triiodothyronine (FT3), and TSH were collected as part of a routine screening programme.
Results: TSH levels increased in both groups at one month, with Group II having a greater TSH than the other. The relationship between TSH at one month and birth weight in the two study groups was significantly unfavourable. The level of FT4 and FT3 at birth and one month were substantially different across groups for APGAR1, APGAR 2, and other measurements.
Conclusions: Thyroid issues are common in preterm babies with a gestational age of 33 weeks and birth weight of 1800 grammes. When thyroid dysfunction was present, the majority of patients exhibited CH and delayed TSH rise, which newborn blood spot screening was unable to identify (NBS).

Keywords: thyroid stimulating hormone, hypothyroidism, preterm neonates

Introduction
The most serious endocrine issues, congenital hypothyroidism (CHT), can lead to severe neurological impairments in newborns if treatment or diagnosis is delayed [1].
Congenital hypothyroidism (CH), a preventable cause of neurodevelopmental disability, strikes around 1 in 2000–4000 babies. The probability of an early identification of this condition has increased, and programmes for newborn screening have virtually eradicated any neurologic adverse reactions. There has been a substantial rise in congenital hypothyroidism reported prevalence during the past 20 years [2].
the skeleton and the nerve system, among other tissues, are stimulated to grow and develop at crucial times by thyroid hormones. It is known to control neurodevelopment, most likely starting in the early stages of foetal life [3].
In premature newborns, there has been research on a specific kind of congenital hypothyroidism. It is uncommon for preterm neonates with this kind of hypothyroidism to be detected until a follow-up test because of a delayed surge in TSH levels. While the precise day varies, this elevation usually takes place between two and six weeks. the vast majority among these infants have a thyroid gland that is physically normal, even though a tiny portion of them suffer thyroid dysgenesis [4].
Primary congenital hypothyroidism (CH) screening for newborns began in the 1970s and has shown to be tremendously successful in lowering the mental impairment brought on by this condition. The most recent modifications to diagnostic patterns, mostly brought on by lower TSH cutoffs and higher preterm infant survival rates [5].

Congenital hypothyroidism (CH) screening using the TSH test technique has been authorised by the Ministry of Health and Population of Egypt (MOHP) [6].

In order to allow for quick treatment of afflicted newborns, In order to detect congenital hypothyroidism during the first 72 hours following delivery, newborn screening programmes were developed. To detect a late surge in thyroid stimulating hormone, a second examination is required a few weeks later in specific neonate subpopulations when the initial screening may not be enough (TSH) [7].

Delayed TSH elevation (dTSH) prevalence was significantly higher LBW newborns (1500–2499 g) and VLBW neonates (1000–1499 g) compared to normal BW (>2500 g) newborns [8].

It is recognised that disorders, including topical iodine usage Immaturity of the hypothalamus-pituitary-thyroid axis in premature neonates, and other drugs can all contribute to delayed thyroid dysfunction. Hence, it is strongly advised that hospitals undertake further thyroid function tests (TFTs) on children who were born severely prematurely [9].

By identifying a delayed rise in thyroid stimulating hormone in preterm neonates with gestational age (33 weeks) and birth weight (1800 gramme) at age of one month, this study intended to determine whether cases of congenital hypothyroidism may be overlooked by the current screening programme.

Patients and Methods

50 preterm neonates with gestational ages ≤ 33 weeks and birth weights ≤ 1.8 kg participated in this prospective research. Patients were split into two equally sized groups: Low birth weight (LBW) preterm neonates make up group one (1.5:1.8 kg). Preterm infants with very low birth weights (VLBW) (less than 1.5 kg) comprise group 2. Neonatal Intensive Care Unit (NICU) at Tanta University Hospital hosted the study from December 2019 to December 2020.

After receiving clearance from Tanta University Hospitals' Ethics Committee, the study was carried out. The parents' informed written consent was acquired.

Exclusion criteria were full term newborns, neonatal mortality < 48 h of life and newborn with CHD, congenital anomalies, IDM.

Both groups underwent careful history taking (prenatal history, postnatal history, mode of delivery, instruments used, resuscitation data and Apgar score at 1&5 minutes), clinical examination (gestational age, body mass, height, width, and other physical characteristics, as well as sex and vital signs) and laboratory Investigations:

a) Neonatal Thyroid Screening (NTS)

TSH level is the first screening according to Egyptian National Screening Program. Using a dried blood spot on filter paper obtained from a prick heel capillary blood sample, all 3- to 7-day-old newborns were tested. ELISA, or enzyme-linked immunosorbent test, was used to quantify TSH (ELISA).

If the concentration of neonatal TSH (NTSH) was less than 15 u/ml, samples were deemed positive. A second dry sample was obtained within two days to be used for a new NTSH measurement if the initial value ranged from 15 to 40 u/ml. If the second NTSH was less than 15 u/ml, the samples were deemed positive and submitted for a confirmation test. Patients with a TSH level over 40 u/ml were submitted for confirmation testing and did not require another dry sample.

Using venous blood specimens were collected on the referral day from the cubital vein, serum T4 and TSH levels were assessed during the confirmatory test at the ministry of health and population's central lab. Without awaited confirmation from the confirmatory tests, treatment was started for newborns whose TSH levels were above 40 u/ml and those whose second dry spot sample levels were below 15 u/ml.

b) Thyroid Function Tests (TFTs)

Free Triiodothyronine Level (FT4), Free Thyroxine Level (FT4), and Thyroid Stimulating Hormone (TSH) (FT3).

Two TFTs were performed on each infant participant in the trial to measure their levels of TSH, free thyroxine (FT4), and free triiodothyronine (FT3).Regardless of the outcomes of the first TFT, it was repeated in the fourth week after delivery. Chemiluminescent microparticle immunoassay was used to assess the levels of serum TSH, FT4, and FT3.

Statistical analysis

The SPSS 25 statistical analysis programme was used (IBM Inc., Chicago, IL, USA). In order to determine whether parametric or nonparametric statistical testing should be utilisedemploying histograms and the Shapiro-Wilks normality test, it was determined how the quantitative data were distributed. The ANOVA test was performed to compare the parametric variables between the three groups, and the post hoc (Tukey) test was utilised to assess each pair of groups independently. The mean and standard deviation were used to represent parametric variables (SD). Non-parametric variables were assessed using the Kruskal-Wallis test and provided as the median and interquartile range (IQR). Thereafter, each pair of groups was compared using the Mann-Whitney (U) test. The Chi-square test was used to conduct a statistical analysis on categorical data, which were then shown as frequency and percentage. Both the receiver operating characteristic curve (ROC) and the Pearson's product correlation coefficient were used. The threshold for statistical significance was a two-tailed P value of 0.05.

Results:

Error! A bookmark self-reference that is invalid. compares the two groups under study based on anthropometric measurements and demographic information.

Table 1: The differences in patient characteristics between the two study groups

	Group I (n = 25) No (%)	Group II (n = 25) No (%)	P value
Gender			
Male	12 (48.0%)	13 (52.0%)	0.777
Female	13 (52.0%)	12 (48.0%)	
Gestational age (week)			
Mean ± SD.	32.44 ± 0.51	29.04 ± 1.24	<0.001*
Mode of delivery			
Vaginal delivery	12 (48.0%)	9 (36.0%)	0.390
Cesarean delivery	13 (52.0%)	16 (64.0%)	
Birth weight (kg)			
Mean ± SD.	1.64 ± 0.08	1.27 ± 0.10	<0.001*
Birth length (cm)			
Mean ± SD.	42.17 ± 1.23	38.64 ± 1.02	<0.001*
Head circumference			
Mean ± SD.	26.23 ± 0.96	26.06 ± 0.98	0.524

The following data are presented as mean± SD or frequency (%), with a minimum significance level of 0.05.

Table 2 shows that there were no statistically significant differences for APGAR 1, APGAR 2, prenatal history (DM, HTN, and PROM), or routine testing between the two research groups.

Table 2: Comparison of the two study groups based on Apgar scores, prenatal histories, and routine tests

	Group I (n = 25)	Group II (n = 25)	p-value
Apgar score			
1st (Mean ± SD.)	4.80 ± 0.76	4.32 ± 0.95	0.054
2nd (Mean ± SD.)	7.76 ± 0.83	7.44 ± 0.92	0.202
Prenatal history			
DM	4 (16.0%)	2 (8.0%)	^{FE}p=0.667
HTN	6 (24.0%)	4 (16.0%)	0.480
PROM	5 (20.0%)	4 (16.0%)	^{FE}p=1.000
Routine investigations			
Hemoglobin	9.40 – 16.70	8.70 – 16.30	0.170
TLC (x10^3)	13.86 ± 6.77	13.01 ± 4.73	0.915
Platelet count (x10^3)	232.32 ± 157.68	229.0 ± 144.73	0.985
CRP	23.76 ± 29.10	21.52 ± 28.18	0.930
Urea	27.08 ± 7.0	26.24 ± 7.04	0.553
Creatinine	0.78 ± 0.32	0.66 ± 0.27	
Total serum bilirubin	8.12 ± 3.91	9.46 ± 3.06	0.184
Direct serum bilirubin	0.47 ± 0.32	0.63 ± 0.34	0.088

The mean, SD, or frequency (%) of the data are reported. Fisher Exact test, or FE. The abbreviations DM, HTN, PROM, TLC, and CRP stand for Diabetes Mellitus, Hypertension, Premature Rupture of Membranes, and Total Leucocytic Count, respectively.

Group II saw a statistically significant increase in TSH (mu/L) compared to group I at one month (P 0.001), and both groups experienced an increase compared to birth (P 0.001). In terms of FT4 (ng/dl) and FT3 (pg/ml) levels, there was no statistically significant difference between the two analysed groups at birth and one month, nor was there a difference between the levels of FT4 and FT3 in either group Table 3.

Table 3: TSH, Free T4, and Free T3 Levels in the Two Research Groups at Different Follow-Up Periods are compared

	Group I (n = 25)	Group II (n = 25)	p-value
TSH (mu/L)			
At birth			
Normal (2.7 – 26.5)	25 (100.0%)	25 (100.0%)	–
Abnormal	0 (0.0%)	0 (0.0%)	
Mean ± SD.	4.0 ± 1.40	4.29 ± 1.34	0.084
At 1 month			
Normal (1.2 – 13.1)	23 (92.0%)	22 (88.0%)	^{FE}p= 1.000
Abnormal	2 (8.0%)	3 (12.0%)	
Mean ± SD.	9.53 ± 4.06	14.61 ± 17.98	<0.001*
$^{Z}p_1$	<0.001*	<0.001*	
FT4 (ng/dl)			
At birth			
Normal (2.2 – 5.3)	25 (100.0%)	25 (100.0%)	–
Abnormal	0 (0.0%)	0 (0.0%)	
Mean ± SD.	2.90 ± 0.54	2.79 ± 0.30	0.553
At 1 month			-
Normal (0.9 – 3.4)	25 (100.0%)	25 (100.0%)	–
Abnormal	0 (0.0%)	0 (0.0%)	
Mean ± SD.	2.61 ± 0.32	2.71 ± 0.19	0.053
$^{Z}p_1$	0.071	0.119	
FT3 (pg/ml)			
At birth			
Normal (1.8 – 7.6)	25 (100.0%)	25 (100.0%)	–
Abnormal	0 (0.0%)	0 (0.0%)	
Mean ± SD.	4.33 ± 0.47	4.06 ± 0.66	0.096
At 1 month			
Normal (2.93 – 5.08)	25 (100.0%)	25 (100.0%)	–
Abnormal	0 (0.0%)	0 (0.0%)	
Mean ± SD.	4.22 ± 0.49	3.87 ± 0.75	0.057
$^{t0}p_1$	0.213	0.282	

The following notations are used to present data as mean, SD, or frequency (percentage): t0: Paired t-test; Z: Wilcoxon signed ranks test; FE: Fisher Exact; p: p value for comparison between the examined groups; p1: p value for

comparison between at birth and at 1 month in each group; *: Significantly significant at p 0.05; Thyroid-stimulating hormone is referred to as TSH. Free triiodothyronine is referred to as FT3. Free thyroxine is referred to as FT4.

In groups 1 and 2, there was a substantial inverse relationship between TSH and birth weight at birth and at one month. Table 4

Table 4: Correlation between gestational Anthropometric measurements with thyroid function in group 1 and 2

		Gestational age (week)		Birth weight (kg)		Birth length (cm)	
P value							
		group 1	group 2	group 1	group 2	group 1	group 2
TSH (mu/L)	At birth	0.328	0.507	0.051	0.028*	0.302	0.930
	At 1 month	0.752	0.141	0.018*	0.038*	0.963	0.379
FT4 (ng/dl)	At birth	0.221	0.897	0.737	0.679	0.116	0.175
	At 1 month	0.295	0.963	0.534	0.189	0.671	0.141
FT3 (pg/ml)	At birth	0.052	0.302	0.023*	0.039*	0.036*	0.381
	At 1 month	0.360	0.315	0.491	0.823	0.992	0.210

Data are presented as mean, SD, or frequency (%) for the following information: TSH, FT3, and FT4 are abbreviations for thyroid-stimulating hormone, free triiodothyronine, and free thyroxine hormone, respectively.

Discussion

The main finding of our study was that there was no statistically significant difference between the two groups in terms of APGAR 1 and APGAR 2, as indicated by p values of 0.054 and 0.202, respectively. There was no statistically significant difference between the two groups in terms of prenatal history of DM, HTN, or PROM. For regular laboratory measurements, there No statistically significant difference existed between the two research groups either.

TSH (mu/L) levels between the two examined groups at birth are not statistically different (p value = 0.946), however there is a difference after one month since group II's TSH levels are higher. TSH was higher (p<0.001), and there is a difference between the two groups' serum TSH levels at birth and one month. In one month, the TSH levels in both groups had increased (p<0.001). When it comes to TSH levels at birth, there are no abnormalities found in either group. Two neonates (8.0%) from group 1 and three (12.0%) from group 2 have abnormally high TSH levels at one month.

What triggers the initial and delayed TSH spike in ELBWIs is still a mystery. ELBWIs are more likely to experience morbid conditions including prenatal hypoxia, infection, surgery, and exposure to medications that inhibit thyroid function, which can result in transient hypothyroxinemia of prematurity (THOP). The hypothalamic-pituitary-thyroid axis has not yet matured in extremely preterm babies, therefore the thyroid gland is unable to release adequate thyroid hormones in response to these pressures. As a result, the presence of THOP in very unwell ELBWIs may be an epiphenomenon of these morbidities and hence not be regarded a thyroid disease (NTI). In their investigation, despite the fact that dopamine is known to reduce TSH production before the initial thyroid function tests (TFT), In addition to perinatal asphyxia, all neonates with early TSH elevations required ongoing ventilation and intubation, and 80% of the babies were subjected to dopamine (performed at a mean of 8.6 postnatal days). Also, neonates with early TSH elevation had significantly lower rates of prenatal steroid use and poorer Apgar scores at 5 minutes when compared to newborns with later TSH elevation and normal controls. While normal at a mean of 7.3 postnatal days, delayed TSH increase was seen with follow-up TFTs at a mean of 36.0 postnatal days following the initial Serum levels [10].

Woo *et al*. research. 's [11] further demonstrated that CH with a delayed TSH increase occurred in 1 in 58 ELBW, 1 in 95 VLBW, and 1 in 30 329 babies weighing less than 1500 grammes (p<0.0001). Although having a higher frequency of head circumferences below the 10th percentile in infants delivered to VLBW who had CH and a delayed TSH rise (p<0.05), their average head circumferences, weights, lengths, and developmental scores were equivalent to those of matched control children. Three babies received short-term levothyroxine replacement.

Also, in the research by Vigone *et al*. [12], the first screening revealed thyroid stimulating hormone rise in 21.7% of patients, while the second screening revealed it in 73.9% of patients. A third screening test revealed one patient (4.4%); 21 individuals had a eutopic thyroid and thyroid dysgenesis in 3 individuals. At reevaluation, 5 patients (23.8%) had chronic hyperthyrotropinemia (s-TSH 5-10 mU/L), 5 patients (23.8%) had permanent hypothyroidism (serum-thyroid stimulating hormone [s-TSH] >10 mU/L), and 11 newborns (52.4%) had transient hypothyroidism (s-TSH 5 mU/L). The main clinical features of patients with chronic hypothyroidism were one case of assisted reproduction, two twins, two petite for gestational age, one case of maternal thyroiditis, and two patients with malformations/syndromes. They concluded that early delivery is a significant risk factor for congenital hypothyroidism with eutopic thyroid. The progression of congenital hypothyroidism in preterm babies remains unclear. These findings emphasise the importance of diagnostic reevaluation to make the accurate diagnosis and show the large incidence of transient hypothyroidism in preterm neonates.

One of the 48 children in the Cavarzere *et al*. trial was a preterm female infant (GA 25 weeks, BW 400 g) who developed a severe case of necrotizing enterocolitis and died during the newborn phase. The remaining 27 individuals began using l-T4 therapy for congenital hypothyroidism with delayed TSH increase. Twenty of them at newborn screening showed isolated hyperthyrotropinemia and did not require treatment. Half of the newborns who had hyperthyrotropinemia during neonatal screening were labelled "false positives" when their TSH levels were assessed, whilst the other half still had elevated TSH levels (>6 U/L) and were believed to have subclinical hypothyroidism.

TSH levels in the blood ranged from 0.228 mIU/L to 100 mIU/L (mean: 5.91 13.838), whereas T4 levels were

between 0.91 ug/dL and 19.70 ug/dL. (mean: 9.89 3.72) in a research by Sardana *et al*. In 10 (4.2%) newborns, elevated TSH was discovered, however not substantially more frequently in females (7) than in men (3).

According to our findings, there is a substantial inverse relationship between TSH at one month and birth weight in group 1 when it comes to the link between prenatal anthropometric measures and thyroid function. Considering group 2's link between thyroid function and gestational anthropometric measures; TSH at birth and at one month has a strong negative connection with birth weight.

Our findings were corroborated by a research by Yoon *et al*. [15], who reported that compared to babies with an instantaneous TSH rise and normal controls, newborns with delayed TSH elevation had statistically significantly lower GA and birth weight.

Heo *et al*. 's infants were subjected to a univariate regression analysis, which showed that Bwt 2,000 g, NICU admission, singleton birth (p = 0.043 vs. twin births and p = 0.001 vs. triplet births), vaginal delivery, congenital heart disease, congenital anomaly, exposure to ICM, and history of surgery were significant risk factors for dTSH. In a multivariate-adjusted model, it was shown that Bwt 2,000 g (OR 2.7, p = 0.002), triplet delivery (OR 0.3, p = 0.015 vs. singleton), and congenital abnormalities (OR 4.1, p = 0.001) were all highly significant predictors of the occurrence of dTSH.

Conclusions

Thyroid issues are common in preterm babies with a gestational age of 33 weeks and a birth weight of 1800 g. The majority of thyroid disease patients had CH with a delayed TSH spike, which NBS missed.

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