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Original Article

Screening for Thyroid Dysfunction among Preterm Infants at Manfalout General Hospital, Assiut, Egypt

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Abstract

Background: Neonatal hypothyroidism is a serious endocrinal disorder that must be diagnosed promptly to avoid irreversible neurological deficits. **Aim of work:** screening of all preterm infants for thyroid dysfunction. **Patients and methods:** All preterm infants enrolled to this study were subjected to thorough history taking and complete physical examinations. Investigations: initially screening for hypothyroidism was done according to Egyptian screening program and serum TSH, T4, and free T4 were done within the 1st week of life and repeated at the end of 2nd and 4th week of life for those with abnormal results only. **Results:** Abnormal thyroid function was detected in 178 (50%) preterm infants. Twenty-two infants were excluded from the study. Mean serum levels of TSH, T4 and free T4 were higher among group II infants (more mature) than 1st group (less mature). The mean levels of T4 and free T4 were higher at the end of 4th week of life than their levels during the 1st week of life. Transient hypothyroxinemia was more frequent thyroid dysfunction disorders among both groups (52.5 % and 38 % for 1st and 2nd groups respectively). Neonatal hypothyroidism, transient primary neonatal hypothyroidism, and transient hyperthyrotropinemia were detected in 9 (11.25%), 18 (22.5%), and 11 neonates (13.75%), respectively for the 1st group and observed in 7 (9.2%), 14 (18.4%), and 9 neonates (11.8%), respectively for the second group **Conclusions:** Thyroid dysfunction was moderately common among preterm neonates. Protocol for thyroid function tests among preterm infants is essential.

Key words: Thyroid dysfunction, prematurity, screening.

Introduction

Thyroid dysfunction especially congenital hypothyroidism (CHT), are the most important endocrinal problems, which might proceed to irreversible neurological deficits in case of delayed diagnosis or treatment of neonates [1]. CHT affects about one infant in every 3,500-4,000 people [2].

Egypt is one of the countries with low iodinated salt intake and a substantial number of neonates suffering from iodine insufficiency, according to UNICEF [3]. The Egyptian Ministry of Health and Population (MOHP) has approved the use of the TSH assay method to screen for congenital hypothyroidism (CH) [4]. For healthcare professionals, an open interview questionnaire was employed, as well as an abstraction checklist form to assess the program's coverage rate based on records of live births and positive instances. For the years 2007, 2008, and 2009, the program's coverage rates were 92.4 percent, 91.7 percent, and 90.9 percent, respectively. At the age of 7-14 days, 86.7 percent of the study subjects were screened, and 53.3 percent of cases were verified at this age. Sixty percent of cases began therapy between the ages of 14 and 21 days; 20% and 26.7 percent of cases improved in terms of weight/age and height/age, respectively, and 40% and 26.7 percent in personal-social and problem-solving domains, respectively. Only one-third of pregnant mothers were notified about the test, and their rates of compliance with therapy, scheduled visits, and investigations were 53.3 percent, 26.7 percent, and 86.7 percent, respectively. Although the doctors in the study were aware of the national programme, they lacked expertise of CH diagnosis and treatment, while nurses were unaware of the relevance of health education for mothers. To summarize, the program's coverage is high, and the therapeutic effects are promising. The awareness and understanding of healthcare providers must be strengthened [4]. Thyroid laboratory dysfunction (primarily

sub/hypothyroidism) in mothers is caused primarily by an autoimmune thyroid condition, as evidenced by higher levels of auto-thyroid antibodies (Anti TPO and Anti TG) that have been found to be significant, and these autoimmune antibodies, in turn, increase the rates of maternal miscarriage, neonatal prematurity, and low birth weight [5].

One of the most frequent endocrine illnesses among children is congenital hypothyroidism (CH) [6] and [7]. The majority of cases of CH are caused by thyroid dysgenesis or, less frequently, dyshormonogenesis; hence, newborns with these underlying causes require lifelong hormone replacement [8] and [16]. Some of those identified with CH during the neonatal period, however, have a temporary thyroid malfunction and can thus quit taking medication following a 3-year trial off-therapy. The prevalence of transitory hypothyroidism varies amongst research, ranging from 35 to 65 percent [17], [18], [19], [20] and [21]. Premature infants had a higher incidence of hypothyroxinemia, hyperthyrotropinemia, and CH than term neonates [22], [23] and [14]. Especially, transient thyroid dysfunction is more commonly observed in preterm infants [13] and [24]. As a result, more infants are treated to thyroid hormone supplementation than full-term infants, and a significant number of these premature babies can be weaned off the medicine. With thyroid imaging examinations such as thyroid ultrasonography and thyroid scans, a range of diagnostic modalities can be performed in newborn newborns with a diagnosis of CH. These studies, however, are difficult to obtain for little premature newborns in critical care, and they rarely influence the decision to begin treatment. As a result, thyroid hormone replacement medication is typically initiated solely on the basis of the findings of thyroid function tests (TFTs), with no follow-up imaging examinations. As a result, in all newborns who have the underlying cause of permanent hypothyroidism, re-

evaluation of thyroid function to determine the permanence of hypothyroidism is indicated. However, there is limited information on the occurrence of permanent CH in infants who were given thyroid hormone after being born prematurely [13] and [24].

Thyroid dysfunction in preterm neonates can be related to the hypothalamic-pituitary-thyroid axis' immaturity, as well as thyroid hormone synthesis and metabolism, as well as systemic illnesses linked to iodine consumption [25]. The recommended treatment for hypothyroxinemia in neonates younger than 28 weeks is to prescribe levothyroxine (until the age of three years). Levothyroxine medication, conversely, may increase morbidity in newborns with a gestational age of 28 weeks and a normal TSH [15]. Thyroid dysfunction needing treatment with levothyroxine was found in roughly one-fifth of preterm babies born before 32 weeks of pregnancy. At one week after birth, about half of the preterm infants who were given levothyroxine had normal TSH and fT4 levels [26]. Further research in this area is strongly suggested by the Cochrane review [27].

Aim of the Work: screening of all preterm infants delivered at Manfalout General Hospital for thyroid dysfunction.

Methods

Participants and study design

The thyroid function of preterm newborns was assessed in this epidemiological study. This study included all preterm newborns (less than 37 weeks) born between September 2017 and August 2019 (356 preterm infants). We exclude all preterm infants with major congenital anomalies, metabolic errors or life threatening conditions. Also all preterm not came for follow up after discharge or those referred to other hospital or died during study period. Taking a history, prenatal history, maternal disease and drugs, obstetric history, and delivery are all things to consider. Exams include the Apgar score and the Ballard score for estimating

gestational age **[**28]. Anthropometric assessments, resuscitations, and a systemic examination, which includes admission and a treatment plan. TSH, T4, and free T4 are tested within the first week of life, and those with abnormal findings are tested again at the end of the second and fourth weeks of life. Thyroid function problems such as transient hypothyroxinemia, neonatal hypothyroidism, transient primary neonatal hypothyroidism, and transient hyperthyrotropinemia were identified using blood samples from the neonates. The infants with abnormal thyroid function are divided into two groups. Preterm newborns with a gestational age of less than or equal to 31 weeks are classified as Group I. Preterm newborns with a gestational age of more than 31 weeks are classified as Group II.

Thyroid function tests, including TSH, free T4, and T4 levels, were performed on selected newborns through radioimmunoassay on day five of life and at two and four weeks of age. Furthermore, skilled nurses took blood samples (1-1.5 cc) from infants' forearms and transmitted them to a single laboratory.

The occurrence of neonatal hypothyroidism, neonatal hypothyroxinemia, and transient neonatal hypothyroidism was determined using data from blood sample analysis. The typical ranges of thyroid function tests were used to diagnose thyroid function abnormalities [27]**,** and thyroid dysfunction definitions. Abnormal thyroid function was detected in 178 (50%) preterm infants. Twenty-two infants were excluded from the study. Also, missing newborns during the study were 25, 22 and 27 after 21st week, 2nd week and 4th week respectively. Levothyroxine supplementation for persistent or profound TSH elevation or low T4 level is usually recommended. The starting dose for infant with delayed TSH elevation is often lower than the dose used for treatment of typical congenital primary hypothyroidism(8-10

ug/kg/day vs. 10-15 ug/kg/day) while the dose for preterm neonate with obvious primary hypothyroidism is similar to that for term neonate. Neonates with persistent hypothyroidism at the age of 4 weeks were subjected to thyroxin therapy according to protocol for treatment of neonatal hypothyroidism and followed up by pediatric endocrinologist [25, 27].

All enrolled infants are exposed to clinical evaluation, management plan, complications for any infant, and investigations for all infants during the follow-up period.

Outlining and diagnosis of thyroid dysfunction

Thyroid function problems among preterm newborns were diagnosed using determined definitions and normal limits of thyroid function tests in this study.

Low T4 and free T4 levels with a normal TSH level validated transient hypothyroxinemia **[**2] and [14]**.** Furthermore, neonatal hypothyroidism was identified in newborns with elevated TSH levels and low free T4 and T4 levels during the neonatal period (low free T4 and T4, TSH level of 10 mU/L or 20 mU/L with any level of free T4 and T4) [2], [14] and [29]. Transient primary neonatal hypothyroidism was identified when free T4 levels were low or gradually declining, and TSH levels were moderately elevated (>5 mU/L in serial testing within the first month of birth) [2] and [14]. Furthermore, despite normal T4 and free T4 levels, transitory hyperthyrotropinemia was confirmed in newborns with increased TSH levels throughout the neonatal period [2].

Ethical considerations

this study was approved from The Ethics Committee of Faculty of Medicine, Al-Azhar University, Assiut, and written informed consents were obtained from the parents and they informed about the nature and steps of the study.

Statistical analysis

SPSS version 20.0 was used to analyze the data (SPSS Inc., Chicago, IL, USA). Continuous variables having a normal distribution were reported as mean,

standard deviation, and numbers and percentages, respectively. Furthermore, numerical data was equated using the Chi-square, independent t-test, or Mann-Whitney U test, if needed. One-way analysis of variance (ANOVA) was used to compare continuous variables, and $\alpha < 0.05$ was considered statistically significant.

Results

All screened preterm infants were 356. Abnormal thyroid function was observed in 178 (50%) preterm infants. Twenty-two infants (all less than 31 weeks of GA) were either expired or referred to other higher center or not present for follow up and those excluded from the study and the remaining 156 (43.8%) preterm infants are enrolled to the study and classified to 2 groups. Group I :80 infants (22.47%). Group II: 76 preterm infants (21.34%). Among the 1st group: 80 preterm infants with gestational age of ≤ 31weeks and mean birth weight was 1122±140 g. Among the 2nd group, 76 preterm infants with GA > 31 weeks and their mean birth weight were 2130±234. The sociodemographic features among both groups and presented in (table 3 and figure 1), and shows a non-statistically significant differences between both groups as regard gender, Apgar score, antenatal steroid use, and pregnancy induced hypertension. A statistically significant differences were found between both groups as regard birth weight, C/S delivery, gestational DM and pathological chorioamnionitis. Mean serum levels of TSH, T4 and free T4 was higher among group II infants (more mature) than 1st group (less mature), (Table 4). The mean levels of TSH, T4 and free T4 were higher at the end of 4th week of live than their levels during the 1st week of live (table 5). Table 6 shows frequency of TSH, free T4, and T4 levels among study groups at 1st week, end of 2nd week and end of 4th week, where, number of infants with low levels of TSH, free T4 and T4 at 4th week of age were less than its levels at the age of 1st and 2nd week of life. Table 7 and figure 2

shows the thyroid dysfunction disorders among study groups, where transient hypothyroxinemia was more frequent thyroid dysfunction disorders among both groups (52.5 % and 38 % for 1st and 2nd groups respectively). Moreover, among the 1st group, neonatal hypothyroidism, transient primary neonatal hypothyroidism, and transient hyperthyrotropinemia were detected in 9(11.25%), 18 (22.5%), and 11 neonates (13.75%), respectively. Among the 2nd group, neonatal hypothyroidism, transient primary neonatal hypothyroidism, and transient hyperthyrotropinemia were observed in 7 (9.2%), 14 (18.4%), and 9 neonates (11.8%), respectively.

Discussion

After the implementation of a nationwide screening programme, the outcomes of infants with congenital hypothyroidism improved dramatically [30] and [31]. In addition to improving prognosis, the newborn screening programme enabled for the early detection of transitory thyroid dysfunction in children [32]. If a permanent underlying cause of hypothyroidism is not discovered during the newborn period, the diagnosis should be confirmed around the age of three. However, studies show that the incidence of this transitory hypothyroidism varies. [18], [19], [20], [21] and [22]. The considerable variation in reported incidence between studies could be attributable to varied diagnostic criteria such as cut-off values, endemic iodine load, re-evaluation policies after first diagnosis, and the characteristics of the recruited patients. Thyroid dysfunction was discovered in 156 premature. Group I: 80 infants. Group II: 76 infants. Group I preterm infants ≤ 31 weeks gestational age (GA), their mean ± SD birth weight (gm), was 1122±140. Group II: preterm infants more than 31 weeks GA and their mean ± SD birth weight (gm), was 2130±234. In comparison to Chung et al. 2009 [13]**,** the other study shows gestational age was 28.5 weeks [39]. In this regard, Hashemipour et al. (2004),

[10] conducted a large-scale study in Isfahan (Iran), finding that the frequency of CHT was one per 349 live births [11]. The inclusion of near term, preterm, and LBW newborns, as well as infants of normal weight, may have contributed to the low incidence of CHT in the study. As a result, our findings for preterm infants appear to be more credible. The frequency of CHT in VLBW neonates was stated to be 0.75 percent in another study by Mandel et al., 2000, [33] which is inferior to the current study. Similarly, Larson et al. (2003) [34], assessed the frequency of newborn with thyroid function problems to be 0.25 percent, which is lower than two Belgian studies (CHT incidence: 5% and 18% owing to iodine shortage in preterm infants) [35]. TSH levels within the first 24 hours after birth were shown to be decrease in the majority of preterm newborns (8, 20 and 23 mU/L in weeks 24-27, 28-30, and 31-34, respectively) in a study of 72 infants with a gestational age of 24-34 weeks [12]. As a result, it's possible to conclude that premature neonates (particularly in weeks 24-27) have a slight rise in TSH and free T4 levels compared to term newborns, which could be due to the hypothalamic-pituitary-thyroid axis' immaturity in preterm neonates. T4 levels in low-birth-weight (LBW) neonates decrease in the first week of life, similar to term newborns, however this decrease is greater in very-low-birth-weight (VLBW) infants [36]. Consistent with the results of the existing study among the 1st group, neonatal hypothyroidism, transient primary neonatal hypothyroidism, and transient hyperthyrotropinemia were detected in 9(11.25%), 18 (22.5%), and 11 neonates (13.75%), respectively. Among the 2nd group, neonatal hypothyroidism, transient primary neonatal hypothyroidism, and transient hyperthyrotropinemia were detected in 7 (9.2%), 14 (18.4%), and 9 neonates (11.8%), respectively. Previous studies have revealed that transitory hypothyroxinemia is a common

condition in preterm infants, with the seriousness of the illness increasing with lower gestational age. This has been ascribed by some academics to neonatal developmental difficulties [37] and [38]. In addition, multiple investigations have highlighted the significant prevalence of transitory hypothyroidism in preterm and low-birth-weight babies. Neonates with transitory hypothyroidism, on the other hand, are more vulnerable to neurodevelopmental problems. The majority of the neonates were above 30 weeks old. Consistent with our data, the occurrence of hypothyroxinemia and CHT in the first and second groups was 52.5 percent and 50 percent, respectively, which is lower than the study by Chung et al.,2009 [13]**.** This difference could be attributed to the increased gestational age of these infants; nonetheless, therapy with levothyroxine could avert difficulties [39], [40] and [41]. The American Academy of Pediatrics (AAP), [9] and European guidelines are not particular for preterm kids with CH; nevertheless, according to Kanike et al., 2017, [42] the majority of preterm infants with hypothyroidism are treated for three years. There is a significant need for specific criteria for the diagnosis, treatment, and follow-up of transitory hypothyroidism [42]. Consistent with the literature, premature infants with CHT are more prone to develop numerous problems, such as RDS, IVH, and NEC, as documented by Chung et al., 2009 [13]. We found PDA, RDS, and NEC in preterm neonates, which is consistent with earlier research. Our results are susceptible to various constraints, such as a small sample size and a short follow-up period (four weeks), which hampered the importance of our studies. With the rising number of preterm births [43] which are the leading cause of impairment and even death. Saeidi, et al., 2016, [44] determining the prevalence of prematurity consequences such as thyroid function problems appear to be critical in any community. As a result, more research is needed, with a longer

follow-up period and a bigger sample size, to confirm the findings described here.

Limitations

Full term neonates not included: because reference ranges are far away from the preterm ranges. Also, the treatment details were not included in this study.

Conclusions

Thyroid function problems are rather common in preterm infants, consistent with the findings of this study. On premature newborns, thyroid function tests must be performed according to a set of guidelines. Future studies in this area should also use greater sample sizes, according to the experts.

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Author's contributions

Authors 1, 2, 3, 4 and 5 equally contributed in the study concept, design, supervision, methodology, statistical analysis and data collection. Author 6 performed the investigations and laboratory workup and wrote the first draft of the manuscript.

Conflict of interest

The authors have no conflict of interests to declare.

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Table 1: Thyroid function test normal ranges (mean ± SD) in preterm newborns (≤ 31 weeks GA)

Postnatal age (days)	TSH (mu/l)	T4 (ug/dl)	FT4 (ng/dl)	T3 (ng/dl)
7 days	3.6 ± 2.5	6.3±2.1	1.82 ± 0.7	56 ± 24
14 days	4.9 ± 1.2	6.6± 2.3	1.65± 0.4	72 ± 28
28 days	3.6 ± 2.5	7.5 ± 2.3	1.7 ± 0.4	82 ± 31

TSH: thyroid stimulating hormone, FT4: free thyroxine, T4: thyroxine, T3: Triiodothyronine

Table 2: Thyroid function test normal ranges (mean ± SD) in preterm newborns (> 31 weeks GA)

Postnatal age (days)	TSH (mu/l)	T4 (ug/dl)	FT4 (ng/dl)	T3 (ng/dl)
7 days	3.6 ± 4.8	9.4 ±3.4	2.14±0.6	92 ±36
14 days	3.8 ± 5.3	9.1 ±3.5	1.98±0.4	110 ±41
28 days	3.5±3.4	8.9 ±3.0	1.88 ±0.5	120 ±40

TSH: thyroid stimulating hormone, FT4: free thyroxine, T4: thyroxine, T3: Triiodothyronine

Table 3: Sociodemographic characteristics of studied preterm infants

Characteristics	Group I (≤ 31 weeks) N (80)	Group II (> 31 weeks) N (76)	P Value
Birth weight (gm), mean ± SD	1122±140	2130±234	0.021*
Male sex, n (%)	48 (60%)	44 (57.9 %)	0.084
Apgar Score, mean ± SD			
1st min	5±2	5±3	0.062
5th min	7±2	7±3	0.062
Delivery type: C/S, n (%)	62 (77.5 %)	72 (94%)	0.034*
Antenatal steroid n (%)	72 (90%)	60 (78.9)	0.071
Pregnancy induced hypertension, n (%)	9 (11.25%)	11 (14.47%)	0.088
Gestational DM, n (%)	5 (6.25 %)	8 (10.52%)	0.022*
Pathologic chorioamnionitis, n (%)	2 (2.5%)	3 (3.9%)	0.038*

*P value < 0.05: statistically significant

Table 4: Mean serum levels of TSH, T4, FT4 based on GA

Mean ± SD	< 28 weeks N = 8	28- 29 weeks N = 12	30-31 weeks N =60	>31 weeks N =76	P Value
TSH (mu/l)	2.26±1.33	3.79±3.14	4.14±1.44	4.41±3.33	0.08
FT4 (ng/dl)	1.24±0.23	1.41±0.29	1.42±0.31	1.53±0.47	0.04*
T4 (ug/dl)	5.06±2.61	6.24±2.25	8.11±3.04	7.47±2.50	0.01*

*P value < 0.05: statistically significant, TSH: thyroid stimulating hormone, FT4: free thyroxine T4: thyroxine, GA: Gestational age

Table 5: Mean levels of TSH, T4, FT4 during 4 weeks after birth

Mean ± SD	Age 5 of birth	14 days	28 days
TSH (mu/l)	3.85±2.83	5.02±4.73	4.36±2.68
FT4 (ng/dl)	1.39±0.47	1.39±0.65	1.24±0.38
T4 (ug/dl)	6.76±2.75	6.73±2.84	6.12±2.42

TSH: thyroid stimulating hormone, FT4: free thyroxine, T4: thyroxin

Table 6: TSH, T4 and FT4 levels during 4 weeks after birth

Levels	1st Week	2nd Week	4th Week
TSH (mu/l)			
< 5	82	70	66
5-7	28	26	16
7-10	26	20	12
>10	20	15	10
Total	156	131	104
Missing cases	22	25	27
FT4 (ng/dl)			
< 0.7	3	2	2
>0.7	153	129	102
Total	156	131	104
T4 (ug/dl)			
<7	86	71	60
>7	70	60	44
Total	156	131	104

TSH: thyroid stimulating hormone, FT4: free thyroxine, T4: thyroxin

Table 7: frequency of thyroid dysfunction among study groups

Thyroid function disorders	Group I ≤ 31 weeks N (80)	Group II > 31 weeks N (76)
Overall prevalence of thyroid dysfunction	80 (22.47 %)	76 (21.34 %)
Neonatal hypothyroidism	9 (11.25%)	7 (9.2%)
Transient hypothyroxinemia	42(52.5%)	38 (50 %)
Transient 1ry hypothyroidism	18 (22.5%)	14 (18.4%)
Transient hyperthyrotropinemia	11 (13.75%)	9 (11.8%)

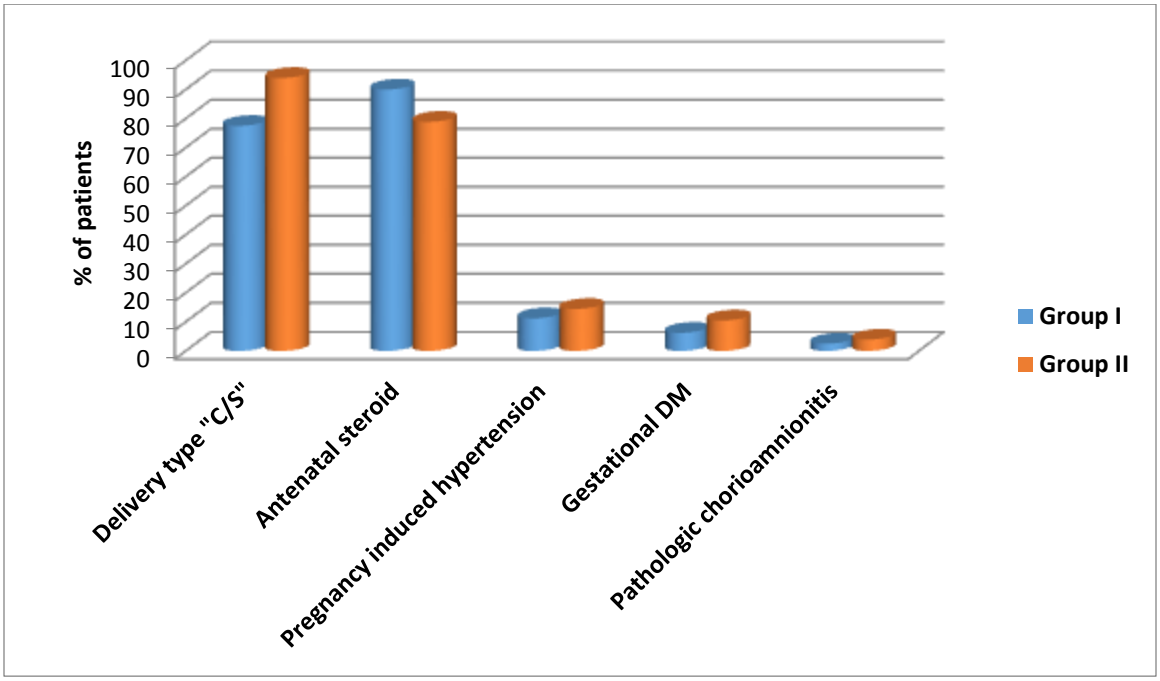

Figure (1): Sociodemographic characteristics of studied preterm infants

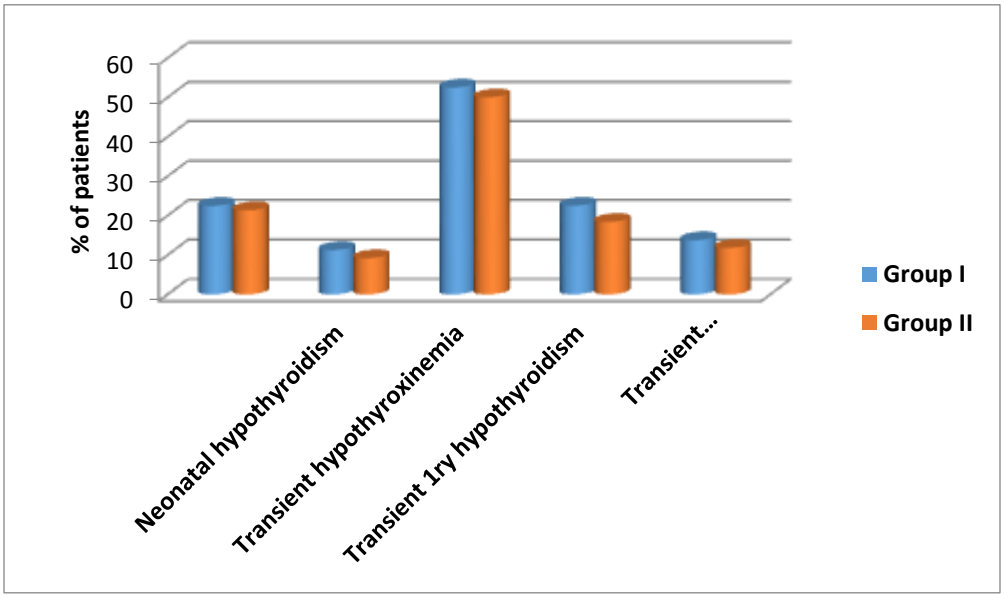

Figure (2): frequency of thyroid dysfunction among study groups

Citation: Amr I. Abo Eleyon Mohamed; Hosny M. Ahmed El-Masry; Alaaeldin A. Hassan; Mohammed M. Sayed Younis; Mohammed A. Aladawy; Alaa M. Hashem. "Screening for Thyroid Dysfunction among Preterm Infants at Manfalout General Hospital, Assiut, Egypt". Annals of Neonatology Journal, 2022(1): 71-90. doi: 10.21608/anj.2021.94162.1036