The Reference Value Of Thyroid Stimulating Hormone For Children Under Age Of Five Years In Nineveh Province, Iraq

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ABSTRACT

Background: Reference ranges of thyroid-stimulating hormones are needed for diagnosing and monitoring children's thyroid disorders based on age and sex.

Aims: The main objective of this study is to establish thyroid-stimulating hormone reference ranges for healthy children below five years old in Nineveh province, Iraq, based on age and sex.

Methods: A cross-sectional study was conducted on one hundred sixty-six healthy children (84 males, 82 females, aged from 2 days to 5 years), and their blood samples were collected at Ibn Al-Atheer and AL-Khansaa Teaching Hospital at Nineveh, Iraq, from October 2023 - March 2024. They were divided into three groups: G1=0–1 months, G2= 1–12 months, and G3=1–5 years. Serum TSH was measured using the enzyme-linked fluorescent assay method (ELFA) by Biomerieux Mini Vidas.

Result: Because of the non-normally distributed data of TSH, reference values were determined using the 2.5% and 97.5 % percentiles. Highly significant difference ($p<0.02$) among mean TSH(µIU/ml) of G 1(5.57±7.86), G 2 (2.67±1.80) and G 3 (2.64±1.72) for males and highly significant difference ($p<0.001$) among mean TSH G 1(6.01±5.94), G 2 (2.18±1.82) and G 3 (2.91±1.71)for females**.**

Conclusions: Higher TSH values are encountered in the G1 with no sex difference of mean TSH, yet the 2.5th%-97.5th% percentile for males is evidently higher than that of females of similar age groups.

Keywords: Reference ranges, pediatric, iodine deficiency, Mini Vidas.

القيمة المرجعية لهرمون المحفز للغدة الدرقية لدى الأطفال دون سن الخامسة في محافظة نينوى، العراق

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الخلاصة

الخلفية: هناك حاجة إلى نطاقات مرجعية للهرمون المحفز للغدة الدرقية في تشخيص ومراقبة اعتلال الغدة الدرقية لدى الأطفال بناء على اعمارهم وجنسهم.

الأهداف: الهدف الرئيسي من هذه الدراسة هو إنشاء نطاقات مرجعية للهرمون المحفز للغدة الدرقية لدى الأطفال الأصحاء دون سن الخامسة في محافظة نينوى، العراق، بناءً على العمر والجنس.

المواد والأساليب: أجريت دراسة مستعرضة على مائة وستة وستين طفل أصحاء (٨٤ ذكرا و ٨٢ أنثى، تتراوح أعمارهم بين يومين إلى ٥ سنوات)، وتم جمع عينات دمهم في مستشفى ابن الأثير والخنساء التعليمي في نينوى، العراق من شهر تشرين الأول ٢٠٢٣ إلى شهر آذار ٢٠٢٤. تم تقسيمهم إلى ثلاثة مجاميع: المجموعة ١ = ٠-١ شهر، المجموعة ٢ = ١-١٢ شهرا، و المجموعة ٣ =١-٥ سنوات. تم قياس الهرمون المحفز للغدة في مصل الدم باستخدام طريقة الفحص الفلوري المرتبط بالإنزيم (ELFA) بواسطة جهاز ميني فيداس Biomerieux Mini Vidas.

النتيجة: بسبب البيانات غير الموزعة بشكل طبيعي للهرمون المحفز للغدة ، تم تحديد القيم المرجعية باستخدام النسب المئوية ٢.٥% - ٩٧.٥%. هناك فرق احصائي ذا قيمة معنوية(ب < ٠.٠٢) بين معدل الهرمون المحفز للغدة(ميكرو وحدة دولية / مل) في المجموعة ١ (٧.٨٦±٥.٥٧) ,المجموعة ٢ (١.٨٠±٢.٦٧) والمجموعة ٣ (١.٧٢±٢.٦٤) للذكور و فرق احصائي ذا قيمة معنوية (ب < ٠.٠١) بين متوسط معدل الهرمون المحفز للغدة في المجموعة ١ (٥.٩٤±٦.٠١), المجموعة ٢ (١.٨٢±٢.١٨) والمجموعة ٣ (١.٧١±٢.٩١) للإناث.

الاستنتاجات: تم استنتاج قيم عليا لهرمون المحفز للغدة الدرقية في المجموعة ١ .و لا يوجد فرق احصائي في معدلات هذا الهرمون بين الجنسين. وقد اظهرت النسبة المئوية ٢.٥% -٩٧.٥% للذكور اعلى من اقرانهم من الاناث.

الكلمات المفتاحية: النطاقات المرجعية، طب الأطفال، نقص اليود، ميني فيداس.

INTRODUCTION

Establishing reference ranges (RRs) in pediatric clinical practice is challenging due to continuous physiological changes during childhood, and accurate pediatric reference values are crucial for accurately interpreting clinical laboratory results, especially for immunochemical analytes [1,2]. Clinical laboratory tests are essential for diagnosing, monitoring, and treating many disorders. However, inadequate reference values for local populations limit the interpretation of the test results [3,4].

Thyroid function is essential for growth and development in children. Small differences in thyroid hormones(THs) balance might cause growth and energy consumption problems and metabolic abnormalities [5].

Serum TSH levels are the most accurate way to diagnose primary hyperthyroidism and hypothyroidism [6,7].

Elevated serum TSH levels around the upper limit of normal reference ranges indicate subclinical hypothyroidism (SH). The SH is defined by an increased TSH level over the upper limit of the reference interval, with normal free thyroxin (FT4) levels within the population RRs [8] since TSH varies throughout countries or ethnic groups [9].

Most children with SH are commonly asymptomatic, and there is no known association with growth impairment or bone abnormality [10].

MATERIAL AND METHODS

Study Design

This study is a cross-sectional study. Serum samples from one hundred sixty-six healthy children, 84 male and 82 female, their ages ranging from 2 days - to 5 years, were collected at Ibn Al-Atheer and AL-Khansaa Teaching Hospitals from October 2023–April 2024 after obtaining ethical approval from the committee of ethics at Nineveh Health Directorate, Nineveh, Iraq, with verbal vocal and written consent of their parents, after clinical excluding of any thyroid problems by a pediatrician.

The enrolled children should have a normal thyroid function assessment and no family or personal history of thyroid disorders. Pituitary alterations such as gigantism, panhypopituitarism, diabetes insipidus, etc.

Premature babies, gestation below 37 weeks, babies who are obese or undersized. Maternal history of thyroid disease or drugs that may affect thyroid function, such as (anticonvulsants, amiodarone, etc.).

Blood Samples Collection

General information, including name, age, residence, and mobile number, was recorded according to the questionnaire. Subjects were classified into three groups: G1= 0-1 months, G2=1-12 months, and G3=1-5 years**.** Approximately 4 mL of venous blood was drawn and centrifuged for 10 min at 3000 rpm.

The supernatant serum was transferred to an Eppendorf tube, which was frozen at -20 °C until the time of analysis in the Biochemistry Department, College of Medicine, Mosul University laboratory. Serum TSH was measured by enzyme-linked fluorescent immunoassay (ELFA) using a kit provided by Biomerieux (France). The detection limit of the kit is 0.05 µIU/ml with RR (0.24-5.4 µIU/ml).

Statistical Analysis

All data are analyzed in a computer using IBM SPSS for Windows version 26.0 (SPSS software, Chicago, ILL). After analyzing the data of TSH, it shows that they were not normally distributed; thus, the Z-test, Mann–Whitney, and Kruskal - Wallis tests were used to show the difference whenever needed. P values ≤ 0.01were considered significant [11].

RESULTS

Table (1) shows no significant difference between the number of males and females for G1, G 2 and G3. Similarly, the mean age of males and females did not significantly differ for all groups. Table (2) shows TSH parameters for the gender of G 1, G2, and G 3 .

Highly significant difference ($p<0.02$) among mean TSH of G 1(5.57±7.86), G 2 (2.67±1.80) and G 3 (2.64±1.72) for males and ($p<0.001$) among mean TSH of G 1(6.01±5.94), G 2 (2.18±1.82) and G 3 (2.91±1.71)for females. There was no significant difference in mean TSH between males and females for each age group: G 1 (p value=0.8), G 2 (p value=0.1), and group 3 (p value=0.4). The G 1 had a considerably higher (2.5th% - 97.5th%) percentile for each sex than the other age groups. TSH levels declined with age.

Table (1) Gender distribution according to age groups.

Parameters		G 1	G 2	G 3
No.(%)	Male	23 (50.0%)	21(47.7%)	38 (52.3%)
	Female	23 (50.0%)	23 (50.0%)	38 (50.0%)
	Total	46 (100.0%)	44 (100.0%)	76 (100.0%)
P-value*		0.9	0.9	0.9
Mean age ±SD (month)	Male	0.28±0.17	3.35±2.76	34.97±11.23
	Female	0.27±0.22	3.57±2.37	35.36±13.34
	Total	0.27±0.20	3.56±2.55	35.17±12.25
P-value**		0.9	0.9	0.9
Range (month)	Male	0.13-0.63	2-10	20-60
	Female	0.07-0.70	1-11	13-60
	Total	0.07-0.70	1-11	13-60

P-value* by Z-test. P-value** by Mann–Whitney test.

Table (2) Different parameters of TSH (µIU/ml) of both genders for age groups

TSH Parameters		G 1	G 2	G 3	P-value*
Mean TSH (µIU/ml) ±SD	Male	5.57±7.86	2.67±1.80	2.64±1.72	0.02
	Female	6.01±5.94	2.18±1.82	2.91±1.71	0.001
	Total	5.79±6.89	2.45±1.76	2.77±1.71	0.001
P-value **		0.8	0.1	0.4	
Median	Male	3.02	1.90	2.07	
	Female	4.03	1.41	2.48	
	Total	3.82	1.80	2.40	
Range	Male	1.12-38.17	0.80-6.30	0.25-6.96	
	Female	0.95-25.41	0.57-5.85	0.47-7.61	
	Total	0.95-38.17	0.57-6.30	0.25-7.61	
2.5th % - 97.5th % percentile	Male	1.12-33.56	0.81-6.30	0.82-6.88	
	Female	0.97-24.01	0.58-5.84	0.53-6.84	
	Total	1.06-22.97	0.67-6.24	0.57-6.81	
95% CI for mean	Male	2.17-8.97	1.89-3.45	2.07-3.21	
	Female	3.44-8.58	1.43-3.00	2.35-3.47	
	Total	3.74-7.84	1.92-2.99	2.38-3.17	

P-value * by Kruskal -Wallis test**.** P-value** by Mann–Whitney test.

DISCUSSION

This study represents the first pediatrics study conducted in Nineveh province, a well-known region with iodine deficiency [12]. Inadequate iodine in the diet is a communal issue. Iodine deficiency affects various sectors of the community, especially pregnant women since iodine is a major microelement in synthesizing THs. [13]. Children under five were included in this study because they are the most sensitive group that showed an alteration in TSH levels, which can affect growth and, more specifically, brain development [14].

Several studies have established thyroid function RRs in the pediatric population from 2012 until now. The Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) study has established age-sex specific RIs for THs using major analytical platforms, including Beckman Coulter Automated chemiluminescence immunoassay (CLIA), Abbott Architect i2000(CLIA), Ortho Vitros(CLIA), Roche cobas electrochemiluminescence immunoassay (ECLIA) and Siemens Atellica(CLIA) [4,15–19].

There is a significant heterogeneity of TSH RRs between studies due to differences in ethnicity, child age, anthropometric characteristics, and iodine status [20,21].

There is no significant difference in mean TSH between males and females of each age group, as shown in Table (2). This was in agreement with Kapelari et al. [22], Bohn et al. [4], and Hübner et al. [23] within our age groups. TSH levels declined with age, especially during the first year of life, which was in agreement with CALIPER studies [4,15–19,24–28], J. Kratzsch et al. [20], Verburg FA et al. [29], A.Lem et al.[30], Najam et al. [31], M. Mutlu et al.[32], Naafs et al.[33], Hübner et al [23] and Elmlinger et al[34].

In this study, the range for TSH (µIU/ml) for boys exhibited much more fluctuation and variability than for girls in the first year. The range for TSH(µIU/ml) of the boys ranged from (1.12-38.17) for the first month and decreased to (0.80-6.30) for the first year of age, while for girls, TSH(µIU/ml) range between (0.95-25.4) to (0.57-5.85) for the first month and the first year respectively. This variability can be attributed to slower neural maturation in boys or undefined biological or environmental/cultural factors [35,36]. This result was in agreement with Legakis et al. [37], who enrolled 2916 full-term healthy infants from birth - 24months of age in Athens, Greece, between 2015 and 2017. Samples were analyzed by using electrochemiluminescence immunoassay.

Kapelari et al , 2008 conducted a study in Innsbruck, Austria. They enrolled 2194 subjects aged 1day-18 years. The automated immunoassay system analyzed samples (Advia, Centaur) [22]. The (2.5th -97.5th)% percentile TSH(µIU/ml) for 22 subjects aged 0 – 1 months was (0.70-18.10), the (2.5th -97.5th)% percentile TSH(µIU/ml) for 24 subjects aged 1-12 months were (1.12-8.21). Apparently, these results differed from that reported in this study, the differences explained by iodine status (iodine sufficient population), instrument used, and small sample size

CONCLUSION

We concluded that there was no sex difference in TSH levels in the three age groups. Higher mean values of TSH are noted mainly in the (0-1 month) age group. The mean TSH values decrease as the age increases. The 2.5th%-97.5th% percentile of males is higher than that of the similar age groups for females.

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