Thyroid Function in Healthy Thai Neonates

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Abstract

Objectives: To construct a normative data for serum thyroxine (T_4), free T_4 (FT_4), triiodothyronine (T_3) and thyrotropin (TSH) in Thai neonates.

Study design: A cross-sectional study of 275 healthy full-term neonates was conducted. Blood samples were obtained from umbilical cords of the neonates and from heel pads of infants aged 1-30 days. Hormone measurements included serum T_4, FT_4, T_3 and TSH.

Results: Mean serum T_4 and FT_4 levels rapidly increased after delivery to the maximum level at 1-3 days of age. Thereafter, they declined to a steady state level within 2-4 weeks. Mean serum T_3 level was very low at birth. The concentration increased 3-5 times and reached a steady state levels within 1 week. In contrast, mean serum TSH declined from birth and the level at 1-3 days of age was slightly less than that of the cord blood. It changed little after 3 days of age. Previous studies have shown a transient TSH surge in the first 24-48 hour of life. TSH surge was not apparent in our study because samples were not obtained from infants <24 hours old. Therefore, if TSH is measured for screening of congenital hypothyroidism, samples should be obtained from umbilical cord or infants aged >48 hours.

Conclusions: This study provides the normative data for thyroid function tests in Thai full-term neonates. These data are useful for detection and verification of hypothyroidism in a screening program for congenital hypothyroidism.

Key word : Thyroid Function, Neonate, Healthy

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Cord blood thyrotropin (TSH) screening for congenital hypothyroidism in Ramathibodi Hospital began in 1993[1]. In other TSH screening programs, blood specimens were obtained from infants aged 2-5 days. Infants with elevated TSH were recalled for thyroid function tests which were obtained between 1 and 3 weeks of age. Thyroid function tests in neonates of different age groups vary considerably[2-5]. However there was no reference ranges for thyroid function tests in healthy Thai neonates and we have been using reference ranges obtained from the US population[2-5].

This study was conducted to obtain reference ranges for thyroid function tests, including total thyroxine (T_4), free thyroxine (FT_4), total triiodothyronine (T_3) and TSH in healthy Thai full-term neonates.

SUBJECTS

Blood samples were obtained from 275 full-term infants with gestational age ranges of 37 to 42 weeks as determined by history and physical examination. These infants had no clinical or laboratory evidence of systemic infection, congenital malformations, birth asphyxia or neurologic insults. None of the subjects received any medications and none had a family history of thyroid disorders. Each infant had blood drawn only once. Iodine containing antiseptics were not used for perineal preparation before delivery.

METHODS

This project was a cross-sectional study. Blood samples were obtained from umbilical cords of the neonates and heel pads of term infants aged 1-30 days. Hormone concentrations were determined by radioimmunoassay using commercial kits manufactured by DPC, USA for T_4 and T_3 and by Amerlite Diagnostic, England for FT_4 and immunoradiometric assay for TSH by DPC, USA.

For T_4, FT_4, T_3 and TSH determinations, the interassay coefficients of variation were 5.2 per cent, 5.8 per cent, 8.8 per cent and 5.5 per cent respectively. The corresponding intra-assay coefficients of variation were 7.0 per cent, 2.8 per cent, 7.2 per cent and 4.1 per cent.

Statistical analysis

Data were expressed as mean, range and standard deviation (SD). Kruskal-Wallis and Chi-square tests were used for comparison among

Table 1. Normal range for total thyroxine (T_4), free thyroxine (FT_4), triiodotyronine (T_3) and thyrotropin (TSH) in Thai neonates.

Age (day)	Total T_4 (μg/dl)			Free T_4 (ng/dl)			Total T_3 (ng/dl)			TSH (mU/L)		
	Mean (n)	SD	Range	Mean (n)	SD	Range	Mean (n)	SD	Range	Mean (n)	SD	Range
Cord blood	8.23 (41)	1.40	5.3-11.8	1.13 (46)	0.18	0.8-1.6	35.7 (41)	16.5	11-81	8.54 (46)	4.48	2.3-24.2
1-3	16.46 (40)	2.73	10.7-22.8	2.39 (40)	0.77	1.3-3.8	143.4 (33)	42.9	85-251	5.60 (34)	2.75	0.9-12.2
4-7	15.44 (44)	2.99	8.7-21.3	1.95 (52)	0.76	1.1-4.6	149.4 (38)	40.9	70-243	5.22 (47)	3.88	1.1-20.5
8-14	13.68 (51)	3.28	7.7-20.1	2.13 (51)	0.51	1.1-3.8	162.8 (50)	35.8	94-239	4.62 (46)	3.70	0.0-20.6
15-21	10.45 (40)	2.71	7.3-16.6	1.59 (38)	0.28	0.7-2.5	147.8 (38)	37.9	79-219	4.20 (40)	2.43	0.8-10.8
22-30	10.61 (42)	2.59	6.6-16.3	1.54 (40)	0.26	1.2-2.4	164.0 (36)	37.0	95-272	4.14 (46)	1.73	1.3-8.4

groups. Multiple comparison between groups were calculated by using non-parametric Mann-Whitney U test. Significant difference was considered when $p < 0.05$.

RESULTS

Data on T_4, FT_4, T_3 and TSH are shown in Table 1, Fig. 1 and Fig. 2. Mean cord blood T_4 and FT_4 levels were 8.23 μg/dl and 1.13 ng/dl; and mean T_3 and TSH levels were 35.7 ng/dl and 8.5 mU/L respectively. Mean serum T_4 and FT_4 peaked at age 1-3 days which were significantly higher than those in cord blood and of infants 4-30 days of age ($p < 0.001$). Transient elevation of T_4 and FT_4 occurred between 1 day and 2 weeks of age and thereafter the levels declined to a steady state. Transient elevation of serum T_4 and FT_4 levels during the first 2 weeks of life may reach as high as > 20 μg/dl and > 4 ng/dl, respectively. Serum T_3 levels were very low at birth and rapidly increased significantly ($p < 0.001$), about 3-5 times within 1-3 days. The levels from 4 days to 30 days of age were not significantly changed ($p > 0.05$). In contrast, TSH levels declined from 8.5 mU/L at birth to 5.6 mU/L at 1-3 days of age ($p = 0.01$) and gradually declined to 4.1 mU/L at 22-30 days of age.

DISCUSSION

Our data confirm the previously described thyroid function tests in neonates[2-5]. Fisher showed that serum TSH increased dramatically to peak levels of 90 to 100 mU/L at 30 minutes following parturition[6]. The TSH surge persists for 48 to 72 hours[6]. In response to the TSH surge, the present results demonstrated that T_4 and FT_4 increased approximately 100 per cent within 24 to 72 hours whereas T_3 markedly increased about 300 per cent because cord blood T_3 concentrations are very low, less than half of maternal levels. Since the main source of serum T_3 is peripheral conversion of serum T_4, this finding is consistent with the previous study that not only T_4 production but also the capacity for conversion of T_4 to T_3 increased in the neonatal period[7].

In contrast, our study shows that TSH levels gradually declined from birth to steady state levels after 3 days. Based on previous study[6], there was a transient TSH surge after birth, reaching the highest level within the first 24 hour of life. In our study on newborns 1-3 days of age, blood samples were usually drawn after 24 hour of life. Therefore, serum TSH levels at 1-3 days of age had no TSH surge and were slightly lower than those in cord blood ($p = 0.01$). Hence, in neonatal thyroid screening, the cut-off point of TSH using cord blood should be greater than that for serum at 1-7 days of age. Our data are comparable to the previous studies[2-5]. The normative data are applicable for full-term neonates only because previous

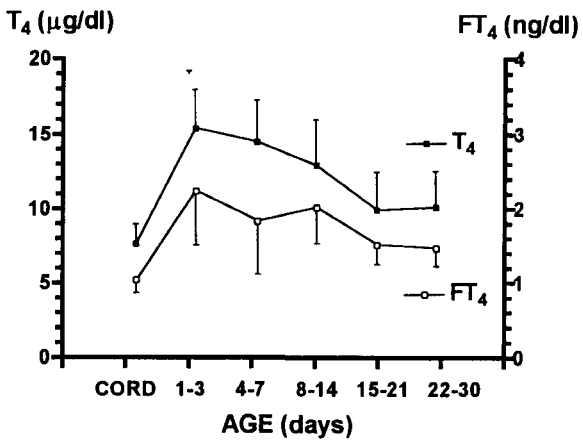

Fig. 1. Mean T_4 + SD and mean FT_4 - SD concentrations in full-term neonates aged 0-30 days.

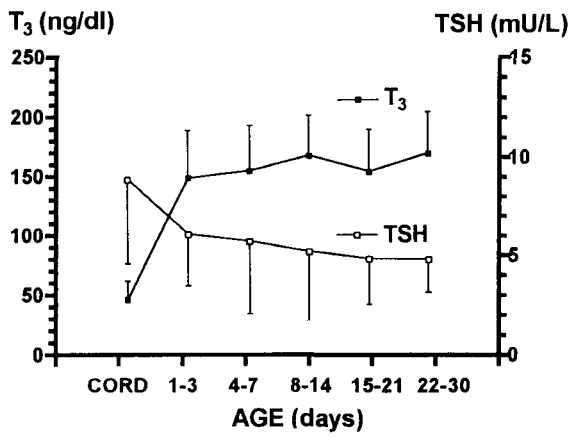

Fig. 2. Mean T_3 + SD and mean TSH - SD concentrations in full-term neonates aged 0-30 days.

studies have shown that the levels of T_4 in preterm neonates might be significantly lower[4,8]. In addition, preterm neonates may have an immature hypothalamic-pituitary-thyroid axis. Therefore, premature neonates with congenital primary hypothyroidism may have a delayed TSH elevation, causing false negative results in TSH screening[9]. Moreover, premature infants have relatively low thyroxine binding globulin (TBG) and low T_4[10], screening program using T_4 would cause false positive results.

At 4 weeks of age, although serum T_4, T_3 and TSH are in steady state levels, the concentrations are higher than those in children and adults whereas serum FT_4 are relatively constant after 2 weeks of age[2]. Compared with adults the elevation of serum T_4 but unchanged serum FT_4 in infants is dued to relatively higher serum TBG.

In conclusion, these normative data of thyroid function tests in Thai neonates allow proper interpretation of thyroid screening for congenital hypothyroidism in Thailand. Newborns with elevated TSH and/or low T_4 levels are recalled for thyroid function tests at ages of 1-4 weeks. Our normative data are also useful for interpretation of thyroid function test during follow-up.

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REFERENCES

1. Rajatanavin R, Chailurkit L, Sriprapadaeng A, et al. Screening for congenital hypothyroidism in Thailand : has its time come? J Med Assoc Thai 1993; 76 (Suppl 2): 2-8.
2. LaFranchi SH. Hypothyroidism. Pediatr Clin North Am 1979; 26: 33-51.
3. Erenberg A, Phelps DL, Lam R, Fisher DA. Total and free thyroid hormone concentrations in the neonatal period. Pediatrics 1974; 53: 211-6.
4. Cuestas RA. Thyroid function in healthy premature infants. J Pediatr 1978; 92: 963-7.
5. Abuid J, Klein AH, Foley TP, Larsen PR. Total and free triiodothyronine and thyroxine in early infancy. J Clin Endocrinol Metab 1974; 39: 263-8.
6. Fisher DA, Odell WD. Acute release of thyrotropin in the newborn. J Clin Invest 1969; 48: 1670-7.
7. Wu SY, Klein AH, Chopra U, Fisher DA. Alterations in tissue thyroxine 5'-monodeiodinating activity in perinatal period. Endocrinology 1978; 103: 235-9.
8. Frank JE, Faix JE, Hermos RJ, et al. Thyroid function in very low birth weight infants : effects on neonatal hypothyroidism screening. J Pediatr 1996; 128: 548-54.
9. Hunter MK, Mandel SH, Sesser DE, et al. Follow-up of newborns with low thyroxine and nonelevated thyroid-stimulating hormone-secreting concentrations : results of the 20-year experience in the Northwest Regional Newborn Screening Program. J Pediatr 1998; 132: 70-4.
10. Thorpe-Beeston JG, Nicolaides KH, Felton CV, Butler J, McGregor AM. Maturation of the secretion of thyroid hormone and thyroid-stimulating hormone in the fetus. N Engl J Med 1991; 324: 532-6.

ค่าปกติของ Thyroid Function Tests ในทารกแรกเกิด

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วัตถุประสงค์ : เพื่อหาค่าปกติของ thyroid function tests ในทารกแรกเกิดที่ครบกำหนด

วิธีการศึกษา : ตรวจเลือดทารกแรกเกิดปกติ จำนวน 275 ราย โดยวัดระดับฮอร์โมน thyroxine (T_4), free T_4 (FT_4), triiodothyronine (T_3) และ thyrotropin (TSH) โดยตรวจเลือดจากสายสะดือและเลือดจากส้นเท้าทารกอายุ 1-30 วัน

ผลการศึกษา : ระดับ T_4 และ FT_4 จะเพิ่มขึ้นอย่างรวดเร็วหลังคลอด โดยมีระดับสูงสุดที่อายุ 1-3 วัน หลังจากนั้นจะค่อย ๆ ลดลงมาอยู่ระดับคงที่ที่อายุ 2-4 สัปดาห์ ส่วน T_3 จะมีระดับต่ำมากเมื่อแรกเกิด แต่จะเพิ่มขึ้น 3-5 เท่าภายใน 1 สัปดาห์หลังคลอด และระดับ T_3 จะค่อนข้างคงที่หลังจากอายุ 1 สัปดาห์ ในทางกลับกัน ระดับ TSH จะค่อนข้างสูงตั้งแต่เกิด และจะลดลงเรื่อย ๆ จนระดับค่อนข้างคงที่หลังอายุ 3 วัน การศึกษาที่ผ่านมาพบว่ามีการเพิ่มขึ้นของระดับ TSH หลังคลอด โดยระดับสูงสุดที่ 0.5-1 ชม.หลังคลอด และจะลดลงอย่างรวดเร็วภายใน 24-48 ชม. ดังนั้นถ้าใช้ระดับ TSH ในการตรวจคัดกรองภาวะพร่องธัยรอยด์ฮอร์โมนแต่กำเนิด ควรตรวจเลือดทารกจากสายสะดือ หรือเมื่อทารกอายุ > 48 ชม.

สรุป : การศึกษานี้แสดงค่าปกติของ thyroid function tests ในเด็กไทยที่เป็นทารกแรกเกิดครบกำหนด ผลการศึกษานี้มีประโยชน์ใช้เป็นเกณฑ์มาตรฐานในการตรวจคัดกรองภาวะพร่องธัยรอยด์ฮอร์โมนแต่กำเนิด และติดตามผล thyroid function tests ในทารกแรกเกิดที่มีความผิดปกติจากการตรวจคัดกรอง

คำสำคัญ : ค่าปกติ, ทารกแรกเกิด, Thyroid Function Test

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