Original Article

Thyroid Function Test in Preterm Neonates: Normative Data

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Abstract

Introduction: Initial surge of thyroid-stimulating hormone (TSH) in neonates increases free and total triiodothyronine (T3) and tetraiodothyronine (T4) in 24–36 hours following birth, and the effect then gradually wanes off. As somatic and intellectual development is dependent on normal thyroid function especially in infancy, normative data in these children may be of immense value to diagnose hypothyroidism in this subset of infants. Comprehensive normative values of thyroid function parameters in preterm neonates are scarcely available. The objective of this study was to determine the normative value of thyroid function parameters in preterm neonates. **Methods:** Preterm neonates (n = 102) born at 34 and 35 weeks of gestation of euthyroid mothers from an iodine-sufficient population were evaluated for T3, T4, free thyroxine (FT4) and TSH during 3–7 days after birth and again after 1 month. The expected date of delivery (EDD) and Ballard score were used to identify the duration of gestation. **Results:** The mean gestational age was 34.7 ± 0.41 weeks. The mean (± SD) for T3 (ng/dl), T4 (µg/dl), FT4 (ng/ml) and TSH (µIU/ml) on days 3–7 following birth was as follows: 156 ± 44.6, 12.8 ± 3.7, 1.50 ± 0.54 and 7.13 ± 6.04, respectively. Around 4 weeks of age, values changed to 104 ± 38.4, 12.1 ± 4.02, 1.46 ± 0.42 and 3.25 ± 2.85, respectively. All parameters changed significantly around 4 weeks, except FT4. None of the parameters were correlated with gestational age or body weight at birth. Normative values for each parameter in percentiles were generated. **Conclusion:** This study generated the normative values of the thyroid function test during the first week and after around 4 weeks of life for premature neonates (born at 34–35 weeks).

Keywords: Preterm neonates, normative data, thyroid function tests

Introduction

India is among the 10 countries with the greatest number of preterm births.[1] The prevalence of preterm birth ranges from 5% to 18% of babies born worldwide.[1] As per the 2014 data, the prevalence of premature birth in India is about 13% of life birth.[1]

Complications related to preterm birth are the leading cause of death among children under 5 years of age and were responsible for approximately 1 million deaths in 2015.[2] These children suffer from a lot of morbidities, such as hypothermia, hypoglycaemia, respiratory distress, hyperbilirubinaemia, feeding difficulties, cardiovascular abnormalities, sepsis and neurodevelopmental anomalies.[3]

Normal physiological parameters in these children are different as compared to term neonates. Thyroid function tests are needed in these children to identify congenital hypothyroidism as well as in the background of certain illnesses.

Thyroid function abnormalities are relatively common in preterm neonates, primarily because of delayed maturation of the hypothalamic-pituitary-thyroid axis.[4] The incidence is approximately 1 in 300 preterm babies with weight less than 1500 g at birth as compared to the overall incidence of congenital hypothyroidism being 1 in 3000.[4] Thyroid-stimulating hormone (TSH) elevation in preterm neonates is often delayed, and it may occur variably between 2 and 6 weeks of age.[4] Additionally, impaired synthesis and metabolism of thyroid hormones, altered demand for thyroid hormone due to non-thyroidal illness and drug administration may be responsible for thyroid function abnormality in preterm neonates.[5] The Indian Society for Pediatric and Adolescent

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Endocrinology (ISPAE) recommended that screening for thyroid function should be conducted for every newborn using cord blood or postnatal blood ideally at 48–72 h of age.[6] Preterm and low birth weight neonates should also undergo screening at 48–72 h of age.[6] These neonates may develop hypothyroidism even when initial thyroid function tests within the first few days of life show normal TSH and free T4 (FT4),[5] necessitating a second assessment which should be at about 2 weeks of age or 2 weeks after the first screening test and possibly not delayed beyond a month.[7]

Keeping in mind the delayed elevation of TSH, normative values for thyroid function parameters after birth and around 4 weeks of life are extremely needed. Normative values are available for neonates from Western countries only, but data for neonates born prematurely are scarcely available.

The relation between maternal iodine status and neonatal thyroid function is also complex. Studies from Ghana suggested that maternal iodine deficiency is correlated to infant thyroid function,[8] whereas a larger cohort of 907 newborns with congenital hypothyroid from the United States did not have significantly different iodine, despite the fact that maternal iodine deficiency is not uncommon in the United States.[9] India is now in the final phase of transition to iodine sufficiency due to effective iodine intervention programme by the Government of India over a long time.[10] Studies from the same population (in which this study was conducted) in another context showed that the mean urinary iodine concentration (UIC) in non-pregnant women was 176 ± 15.7 μg/L reflecting a state of iodine sufficiency in general. UIC (μg/L) in different trimesters of pregnancy in the same population-based study was 205 ± 16.9, 176 ± 14.9 and 182 ± 16.7, respectively.[11]

In this context, this study was undertaken to test thyroid function in preterm neonates born in a population in which all likelihood is iodine-sufficient and develops normative data of thyroid function tests for these preterm neonates at birth as well as around 4 weeks. We also explored whether there was any correlation between individual parameters of thyroid functions and the gestational age or body weight.

Materials and Methods

This prospective observational study was conducted in the Department of Obstetrics and Gynaecology and the Department of Neonatology at the Institute of Post Graduate Medical Education and Research, Kolkata.

The following inclusion criteria were used. The neonates had an Apgar score of at least 7 at 5 minutes of life and had length, weight and head circumference appropriate for the gestational age at birth and were spontaneously breathing on room air and feeding normally. Neonates who did not have any medical or surgical complications or congenital malformations were included. Babies of known hypothyroid mothers or euthyroid mothers on levothyroxine treatment were excluded.

The sample size was calculated assuming an incidence of thyroid dysfunction of 58% after birth[12] using a 95% confidence interval and with a margin of error of 10%. Hence, a total of 94 premature babies were needed for this study. Assuming that 10% of neonates initially screened may not be available for subsequent sampling per protocol, we planned to include 103 premature neonates for the study. Postnatally, povidone-iodine was not used in any infant as per institutional protocol.

Consecutive premature neonates (born at 34–35 weeks of gestation) satisfying the aforementioned criteria were selected. The gestational age was calculated from the date of the last menstrual period (LMP) as stated by the mother. This was then corroborated with the new Ballard maturational score as described below.[13]

Physical maturity based on the new Ballard maturational assessment of the gestational age was conducted by the standard scoring system.[13] The scoring for each neonate was measured on the basis of physical examination of skin texture, presence and quality of lanugos hairs, examination of plantar surface, presence or absence of breast bud and its size, examination of eyes and ears especially the cartilage of pinna and examination of genitals. Each category was scored from -1 to 4 for all except for skin and lanugo hairs which were scored from -1 to 5. The scores ranged from 5 to 50, with the corresponding gestational ages being 26 weeks and 44 weeks. An increase in the maturity score by 5 occurs for is rated with an increase in age by 2 weeks. The Ballard score was assessed by a single expert neonatologist.

If there is a discrepancy between the gestational age based on LMP as stated by the mother and Ballard by more than 2 weeks (or if exact LMP was not available), then the Ballard score was used.

Once the babies were selected for the study, the baby's mother was explained about their participation in the study and consent was obtained. Blood samples were taken between 2 and 7 days of birth. After 1-month period (with a relaxation period ± 3 days), the babies were reevaluated clinically (including weight change) and venous samples for the thyroid function test were collected.

Assay methods

Serum samples were immediately stored at -20°C for subsequent analysis within 1 week unless tested on the same day. Serum TSH, FT4, total tetraiodothyronine (TT4) and total triiodothyronine (TT3) were estimated by the chemiluminescence technique (CLIA) using commercially available kits from Siemens Diagnostics (Germany) with Immulite 1000 Analyzer. The analytical sensitivity and total precision values (as given by providers) were 0.01 μIU/ml and 2.2% for TSH, 0.35 ng/dl and 2.7% for FT4, 0.4 μg/dl and 2.5% for TT4 and 35 ng/dl and 2.2% for TT3. The laboratory reference ranges were TSH (0.4–4 μIU/ml), FT4 (0.8–1.9 ng/dl), TT4 (4.5–12 μg/dl) and TT3 (81–178 ng/dl), and the inter-assay

coefficients of variation (CV) for the assays were 8.9%, 5.5%, 6.7% and 9.3%, respectively, as determined locally.

Statistical analysis

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software (version 21.0; SPSS, Inc. Chicago, IL, USA). The data were tested for normality using the Shapiro-Wilk test. Normally distributed, continuous data are presented as mean value ± standard deviation (SD). The limits of the reference intervals for TSH, FT4, TT4 and TT3 were calculated as 2.5th percentile, 25th percentile, median or 50th percentile, 75th percentile and 97.5th percentile. Student's paired *t*-test was performed for comparing continuous data from the same subjects in two related groups. The correlation between continuous variables was conducted using Pearson's method.

The study was approved by the Institutional Ethics Committee of the Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India, vide letter no Inst/IEC/2018/069 dated 20.11.18. Written informed consent was obtained from the parents of all neonates. The procedures in the study follow the guidelines laid down in the Declaration of Helsinki.

Ethical aspects

The study was approved by the institutional ethics committee (IPGME&R Research Oversight Committee: Memo number: Inst/IEC/2018/069).

Results

The consecutive 102 premature neonates were selected for the study. Among them, 49 (48%) were males and 53 (52%) were females. The mean gestational age (mean ± SD) was 34.7 ± 0.41 weeks. Of them, 64 infants (62.7%) were born at 35 weeks, and 38 neonates (37.3%) were born at 34 weeks. The mean weight (mean ± SD) of the neonates was 2.317 ± 0.35 kg. The mean weight (mean ± SD) at 4 weeks was 3.360 ± 0.60 kg.

Each of these parameters was assessed to develop a percentile chart of normative distribution. This distribution is shown in Table 1. Most importantly, the median of TSH, TT4 and FT4 at birth was 5.02 mU/L, 12.85 µg/dL and 1.38 ng/dL, respectively.

The mean (± SD) TT3 (ng/dL), TT4 (µg/dL), FT4 (ng/dL) and TSH (mU/L) values on days 3–7 of birth are as follows: 156 ± 44.6, 12.8 ± 3.7, 1.50 ± 0.54 and 7.13 ± 6.04, respectively. After around 4 weeks of age, the values changed to 104 ± 38.4, 12.1 ± 4.02, 1.46 ± 0.42 and 3.25 ± 2.85, respectively. The changes after around 4 weeks were statistically significant for TT3 ($P < 0.01$), TT4 ($P < 0.05$) and TSH ($P < 0.01$), as compared to baseline results. However, for FT4, the change was not statistically significant. This comparison is shown in Table 2. None of the parameters was correlated with gestational age or body weight at birth. TT4 concentrations at 3–7 days of age stratified according to birth weight are presented in Table 3.

Discussion

Despite the advancement of obstetric care, the preterm birth is still a global problem and these neonates are more prone to thyroid dysfunction requiring levothyroxine treatment in approximately one-fifth of preterm infants born before 32 weeks of gestation.[5] Studies on congenital hypothyroidism, its screening, prevalence and management in full-term neonates are numerous. Only a few studies are available for preterm neonates, though the prevalence of thyroid dysfunction in this age group is substantial.

The largest and most comprehensive study on thyroid function parameters in premature neonates stratified by gestational age of 23 weeks and more and through day 28 of life was performed by Williams *et al*.[14] In all the subgroups of preterm neonates, TSH decreased (cord blood test) as compared to venous blood TSH around day 28. T3 increased in the first 4 weeks after birth. However, the T4 and FT4 levels decreased from day 7 to day 28 in those born after 30 weeks of gestation. This study also determined the ranges of the normative value of thyroid function at different ages till 28 days of age. The study was performed mainly in Scotland, and TSH was measured by the radioimmunoassay (RIA) method. It may be noted that TSH is not normally distributed in a population but rather displays a skewed distribution.[15] Though the study reported the median value, the other percentiles were not reported. The iodine status of the cohort was not mentioned.

FT4, as determined by direct equilibrium dialysis for infants born between 31 and 36 weeks of pregnancy, was found to be 1.3–4.7 ng/dl, measured during the first week of life in the study by Adams *et al*.[16] The FT4 level and logarithm value of TSH correlated positively with the gestational age. However, this study evaluated the test results performed in the first week of life only. In another study by Clark *et al*.,[17] the reference ranges for thyroid function tests in premature infants beyond the first

Table 1: Normative value of thyroid function parameters of premature neonates (born at 34–35 weeks) at birth and around 4th week of life

Parameters (n=102)	TFT on days 3–7 (percentile)					TFT around 4 weeks (percentile)				
	2.5th	25th	75th	97.5th	Median	2.5th	25th	75th	97.5th	Median
TSH (µIU/ml)	1.69	3.72	8.28	26.45	5.02	0.97	1.68	4.17	13.97	2.87
T3 (ng/dl)	66	128	185	264	152	45	77	122	200	98
T4 (µg/dl)	6.6	10.3	15.0	22.0	12.8	5.4	9.1	14.7	21.7	11.2
Free T4 (ng/dl)	0.76	1.16	1.77	3.10	1.38	0.81	1.20	1.67	2.39	1.33

Table 2: Comparison of thyroid function parameters of premature neonates (born at 34–35 weeks) at birth and around 4th week of life

Parameters (n=102)	TFT on days 3-7 (mean±SD)	TFT around 4 weeks (mean±SD)	*P*
TSH (mu/l)	7.13±6.04	3.25±2.85	<0.001
T3 (ng/dl)	156.18±44.69	104.11±38.47	<0.001
T4 (µg/dl)	12.88±3.73	12.10±4.02	<0.05
FT4 (ng/dl)	1.50±0.54	1.46±0.42	0.87

Table 3: T4 concentrations in premature neonates (born at 34–35 weeks) at 3–7 days of age according to birth weight

Birth weight (Gms)	T4 (µg/dL)
<1500 gms	9.6±2.61
1500–2000 gms	11.9±3.37
1500–2000 gms	13.4±4.09
>2500 gms	13.3±3.10

week of life (closest to the 3rd week) were measured. FT4 for premature infants born 28–40 weeks post-conceptionally was 0.8–2.6 ng/dl (n = 161), and TSH was 0.8–12.0 mU/l (n = 135). FT4 was not different among post-conceptional age groups and did not correlate with gestational or postnatal age. Zhu *et al.*[18] reported that the reference intervals for FT4 and TSH for the neonates born at gestational ages between 31 and 36 weeks were 0.798–2.7 ng/dl (10.28-34.87 pmol/l) and 0.68–12.53 mIU/mL in a cohort of 247 Chinese preterm hospitalized infants aged between 8 and 15 days. However, the studies evaluated the thyroid function at a single point of time only.

Carrascosa *et al.*,[19] however, measured thyroid function in the mother and in the cord at delivery and in the 75 healthy preterm infants, 30–35 weeks of the gestational age at 1 hour, 24 hours, 1 week, 3 weeks, 2 months, 4 months, 6 months and 12 months of postnatal age. They concluded that individual thyroid function was similar in healthy pre-terms and full-terms from the first 24 hours of life. TSH usually follows a non-parametric pattern, and they expressed their results in terms of mean (± SD). Normative data in terms of percentile were not provided. Mercado *et al.*[12] also evaluated thyroid function at 24 h, 72 h, 1 week, 3 weeks, 4 weeks, 5 weeks and 6 weeks of age in 108 preterm infants born at 23–31 weeks of gestation.

Apart from establishing the reference ranges (mean ± SD), this study suggests that there is an increasing delay in maturation of the hypothalamic-pituitary-thyroid axis control with increasing prematurity. However, this study was conducted in 1988 (before the era of advanced chemiluminescence) and this study did not report normative data in terms of percentiles. Uhrmann *et al.*[20] in another longitudinal study for up to 3 weeks on 35 preterm infants concluded that normal preterm infants have a pattern of thyroid function qualitatively similar but quantitatively different from that of term infants.

We studied the preterm neonates born at 34–35 weeks at two points. We found that the TSH range (2.5th–97th) was 1.69–26.45 µIU/ml and 0.97–13.97 µIU/ml at birth and around 4 weeks, respectively, which is not very different from other studies. This was true for FT4 also for which the range (2.5th–97th) was 0.76–3.10 ng/dl and 0.81–2.39 ng/dl at birth and around 4 weeks, respectively.

Adam *et al.*[16] found a correlation between the gestational age and FT4 and logarithm of TSH, but we could not find any such relation. Though Romagnoli *et al.*[21] noted no significant influence of birth weight on T4 and TSH, Frank *et al.*[22] observed median T4 concentrations for each weight group (in 250 gm increments) increased progressively and significantly up to 2500 gm. Thyrotropin concentration correlated inversely with birth weight and gestational age in the study by Korada *et al.*[23] However, such correlation was not present in our study.

Limitations of the study

Though the study has a sufficient number of subjects to establish normative data, it would have been even better if we had a greater number in each stratum including inclusion of more premature births. Additionally, the majority (62.7%) of the newborns were born at 35 weeks of age, and 38 neonates (37.3%) were born at 34 weeks of age. Also, this is a single-centre study and may not reflect accurately the thyroid function parameters of neonates from other ethnic populations and population with varying iodine status.

Conclusion

This study generates the normative values for the thyroid function test during the first week and after around 4 weeks of life of neonates born prematurely at 34–35 weeks. In the background of increased prevalence of several illnesses in this age group and because of the fact that normal thyroid function is extremely essential for somatic and intellectual development, normative data of thyroid function tests may be of immense value in preterm neonates as the deficiency could be adequately corrected with early institution of an effective therapy which might prevent important morbidities related to the thyroid dysfunction.

Acknowledgment

None.

Authors' contribution

S.G. conceptualized and supervised the study. D.M. selected the patient and conducted the test. P.M., D.M. and S.G. involved in data analysis. S.G., D.M., B.S., S.S., and P.M. prepared the manuscript.

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Conflicts of interest

There are no conflicts of interest.

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