Study Of the Thyroid Hormone Profile in Preterm Small for Gestational Age and Appropriate for Gestational Age Infants in A Tertiary Care Hospital

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ABSTRACT

Background: Thyroid hormone play a key role in normal growth and development of children especially in their first two years of life. Untreated congenital hypothyroidism can lead to intellectual disabilities and developmental abnormalities.5Even transient hypothyroxaemia in early neonatal period can cause neurologic and mental problems.6Thyroid dysfunction is more common in preterm neonates when compared to term babies. Additional to prematurity, being small for gestational age further affects the cognitive and sensorimotor functions of an infant. There are very few studies that showed altered thyroid hormones in the first week of life in preterm SGA, so further studies are required. We did the present study to compare thyroid hormone profile among preterm SGA and preterm AGA and to see if being SGA makes the preterm babies more susceptible to thyroid dysfunction and if any comorbidities of the preterm newborns have any association with their thyroid hormone profile.

Methods: It was designed to study thyroid hormone profile and frequency of thyroid dysfunction in preterm SGA and AGA infants. Study also assessed the association of neonatal clinical conditions like low APGAR score, intraventricular haemorrhage, necrotising enterocolitis, congenital heart diseases and NICU intervention such as surfactant administration, and use of medications (steroids, dopamine and furosemide) with thyroid hormone profile in preterm SGA and AGA infants. Observational, Cross-Sectional Study was done for 18 Months in Neonatal intensive care unit, Krishna Institute of Medical Sciences, Karad. All preterm newborns (GA <37 Weeks) admitted to the neonatal intensive careunit, Krishna Institute of Medical Sciences, Karad including both preterm SGA and preterm AGA were included in the study. The Thyroid function test was performed on Day 4 of life in preterm SGA and preterm AGA infants in NICU and repeated on Day 14. Thyroid function test (TFT) results, and
INTRODUCTION

Thyroid hormone plays a key role in normal growth and development of children especially in their first two years of life. Thyroid hormone helps in neurogenesis, neuroglial cell differentiation, maturation and migration and in myelination. Several studies suggest that prenatal and early post-natal life are affected by hypothalamo-pituitary-adrenal axis and thyroid function. The hypothalamo-pituitary-thyroid axis formation and maturation begins in utero itself. Early in pregnancy foetus is dependent on maternal thyroid hormone and gradually starts to produce by second trimester, reducing the reliance and remains at lower levels till birth. At birth there is a rapid surge in thyroid stimulating hormone that further helps in production of thyroxine and triiodothyronine hormones. Untreated congenital hypothyroidism can lead to intellectual disabilities and developmental abnormalities. Even transient hypothyroxinaemia in early neonatal period can cause neurologic and mental problems. Therefore, early detection and timely intervention of congenital hypothyroidism is required for best results. With the advent of new born screening we are able to screen for congenital hypothyroidism. Increasing preterm deliveries and advances in neonatal care warrants the need for proper understanding of their physiology and proper thyroid screening guidelines for premature babies. Thyroid dysfunction is more common in preterm neonates when compared to term babies owing to the immature hypothalamo-pituitary-thyroid axis and premature severance of maternal thyroid hormones. The thyroid gland is smaller in preterm neonates with decreased production and iodine storage capacity. Other contributing factors include immature peripheral deiodination, non-thyroidal diseases and or exposure to medications in NICU. Transient hypothyroxinaemia of prematurity is the most common thyroid dysfunction in preterm low birth weight neonates. However permanent hypothyroidism might also occur. Additional to prematurity, being small for gestational age further affects the cognitive and sensorimotor functions of an infant. One study revealed that preterm SGA newborns have higher TSH concentration. Further-more, catch up growth during early childhood for SGA infants and its
Pattern are influenced by hypothyroidism and LT4 replacement therapy. Cianfarani et al found that SGA child with blunted CUG had higher TSH concentration suggesting that thyroid function might affect their postnatal growth. Uchiana et al added that being SGA is a risk factor for transient hypothyroxinaemia with delayed TSH elevation (dTSH) in congenital hypothyroidism in VLBW infants. Further, Chunhua Liu proved that SGA is a risk factor for thyroid dysfunction in preterm newborns. There are very few studies that showed altered thyroid hormones in the first week of life in preterm SGA, so further studies are required. We did the present study to compare thyroid hormone profile among preterm SGA and preterm AGA and to see if being SGA makes the preterm babies more susceptible to thyroid dysfunction and if any comorbidities of the preterm newborns have any association with their thyroid hormone profile.

MATERIAL AND METHODS
This was an observational cross-sectional study conducted in Neonatal intensive care unit, Krishna Institute of Medical Sciences, Karad for 18 months from 1st February 2020 to 31st August 2022. All preterm newborns (GA <37 Weeks) admitted to the neonatal intensive care unit including both preterm SGA and preterm AGA were included in the study. SGA was defined as a birth weight below the 10th percentile for a given GA and sex. AGA was defined as a birth weight between 10th and 90th percentile for a given GA and sex. Preterm neonates admitted after 1 week of age, expired, who developed sepsis or other severe infectious diseases, neonates with maternal thyroid diseases, history of use of Lugols’ iodine or Iodine containing disinfectant or cleaning materials and maternal use of Lithium (antipsychotic)/chemotherapeutic/anti-inflammatory drugs/radiation were excluded. After exclusion, 148 preterm infants (74 SGA and 74 AGA infants) entered into the final analysis. The Thyroid function test was performed on Day 4 of life in preterm SGA and preterm AGA infants in NICU and repeated on Day 14.3ml venous blood sample was drawn into sterile vacutainers and stored at – 20°C, then TSH and FreeT4 assays were done using the automated analyzer (Tosohcompany Japanese make). Demographic profile and relevant information have been collected by using structured Proforma by interviewing mother. The neonatal demographic characteristics included sex, birth weight, gestation, being a twin and mode of delivery. The history of clinical condition such as 5-min Apgar scores, presence of respiratory distress syndrome detected by administration of surfactant, severe intraventricular hemorrhage defined as grade III/IV, necrotising enterocolitis proven clinically/radiologically, and cardiac problems proven by 2decho report, and NICU intervention such as surfactant administration, and use of medications (steroids, dopamine and furosemide), were collected. Thyroid dysfunction is assessed based on standard reference ranges for preterm neonates based on gestation and day of sampling.

Transient hypothyroidism is defined as low FT4 with high TSH levels normalized in subsequent screening.

Transient hypothyroxinemia is defined as low FT4 with normal or low TSH normalized in subsequent screening.

Delayed TSH elevation (dTSH) is defined as TSH elevation in subsequent screening after a normal TFT.

Hyperthyrotopinemia is defined as TSH elevation with normal or elevated FT4 that reverts to normal in subsequent screening.

The data was entered in MS EXCEL spreadsheet. The data was analysed using SPSS version 20. Comparison was made between AGA and SGA Preterm thyroid function test results and unpaired t-test was used to observe if the differences were statistically significant. p< 0.05 was considered as significant.

OBSERVATIONS AND RESULTS
Present study included total 148 participants of which 74 were appropriate for gestational age whereas 74 were small for gestational age. It was observed that among the study participants, in preterm SGA group 64.86% were males and 35.13% were female patients while in preterm AGA group 43.24% were males and 56.75% were female patients. Twin pregnancy was observed in 13.51% of preterm SGA group and 12.16% in preterm AGA group.
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preterm AGA group. Mode of delivery was analysed and it was found that in preterm SGA group 24.32% were delivered by EMLSCS, 2.7% by vacuum assisted vaginal delivery and 72.97% by normal vaginal delivery whereas in preterm AGA group 27.03% were delivered by EMLSCS, 2.7% by elective LSCS, 2.7% by forceps assisted vaginal delivery and 67.56% by normal vaginal delivery. The mean birth weight of SGA group was found to be 1.0369±0.241 and 1.21±0.26kg in AGA group. In preterm SGA group majority belonged to ELBW with 59.45%, followed by 37.83% in VLBW and 2.7% in LBW and in preterm AGA group majority belonged to VLBW with 62.16% followed by 27.03% in ELBW and 10.81% in LBW.

Mean value of TSH was measured to be 5.81mU/L in the SGA group whereas it was relatively less in the AGA group with mean value of 4.42 mU/L. The p value was <0.0001 which was found to be statistically significant. Mean FT4 value in SGA preterms was 1.69ng/dl while in AGA preterms was 1.97ng/dl. (Table 1)

<table>
<thead>
<tr>
<th>TFT</th>
<th>SGA (n 74)</th>
<th>AGA (n 74)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH (mU/L) (presented as mean and standard deviation)</td>
<td>5.81±1.54</td>
<td>4.42±1.44</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FT4 (ng/dl) presented as mean and standard deviation</td>
<td>1.69±0.34</td>
<td>1.97±0.5</td>
<td>0.43</td>
</tr>
</tbody>
</table>

In this study transient hypothyroidism was seen in 1 SGA preterm and 2 AGA preterms, transient hypothyroxinaemia was seen in 3 SGA preterms and 5 AGA preterms, hyperthyrotopinemia was seen 4 each in SGA and AGA preterms and 1 case of delayed TSH elevation in preterm SGA group though none was statistically significant. (Table 2)

<table>
<thead>
<tr>
<th>Thyroid dysfunction</th>
<th>SGA(Frequency)</th>
<th>AGA(Frequency)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient Hypothyroidism</td>
<td>1</td>
<td>2</td>
<td>0.64</td>
</tr>
<tr>
<td>Transient hypothyroxinaemia</td>
<td>3</td>
<td>5</td>
<td>0.45</td>
</tr>
<tr>
<td>dTSH</td>
<td>1</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Hyperthyrotopinemia</td>
<td>4</td>
<td>4</td>
<td>0.44</td>
</tr>
</tbody>
</table>

In the study low APGAR score at 5 minute (score <7) was seen in 18.91% in SGA preterms and 8.1% in AGA preterms. We observed statistically significant higher TSH (7.46±0.66) in low APGAR preterm SGA babies and statistically significant higher TSH (7.74±1.22) in low APGAR preterm AGA babies. (Table 3)

<table>
<thead>
<tr>
<th>APGAR score</th>
<th>SGA preterm TSH (mean±SD)</th>
<th>AGA preterm TSH (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>7.74±1.22</td>
<td>7.46±0.66</td>
</tr>
<tr>
<td>Normal</td>
<td>4.12±1.02</td>
<td>5.42±1.43</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 4 shows that 18.91% SGA preterm and 29.72% of AGA preterms had congenital heart disease, 10.81% SGA preterm and 2.7% of AGA preterms had severe intraventricular haemorrhage and 9.5% SGA preterm and 5.4% of AGA preterms had necrotising enterocolitis.

**TABLE 4: Distribution of clinical conditions and drug administration in preterm SGA and AGA group**

<table>
<thead>
<tr>
<th>Clinical conditions</th>
<th>SGA Frequency (Percentage)</th>
<th>AGA Frequency (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD</td>
<td>14(18.91%)</td>
<td>2(29.72)</td>
</tr>
<tr>
<td>IVH</td>
<td>8(10.81%)</td>
<td>2(2.7%)</td>
</tr>
<tr>
<td>NEC</td>
<td>7(9.5%)</td>
<td>4(5.4%)</td>
</tr>
<tr>
<td>Surfactant</td>
<td>8(10.81%)</td>
<td>18(24.32%)</td>
</tr>
<tr>
<td>administration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>4(5.4%)</td>
<td>6(8%)</td>
</tr>
<tr>
<td>Dopamine</td>
<td>2(2.7%)</td>
<td>2(2.7%)</td>
</tr>
<tr>
<td>Furosemide</td>
<td>4(5.4%)</td>
<td>2(2.7%)</td>
</tr>
</tbody>
</table>

TSH was on higher side in severe intraventricular haemorrhage (6.65±1.8) in preterm SGA group and (6.65±1.8) in preterm AGA group. (p value 0.003 in AGA group.) Clinical conditions like CHD, IVH, NEC did not affect FT4 values in preterm SGA and AGA group. 10.81% SGA preterm and 24.42% of AGA preterms required surfactants, 5.4% SGA preterm and 8% of AGA preterms used steroids, 2.7% SGA preterm and 2.7% AGA preterms used dopamine and 5.4% SGA preterm and 2.7% of AGA preterms used furosemide. (Table 4) Medications like surfactant administration, usage of steroids, dopamine and furosemide did not affect TSH and FT4 concentration in preterm SGA and AGA in the present study.

**DISCUSSION**

Normal development of brain requires proper thyroid functioning, especially in the first two years postnatally. Therefore, early identification and proper treatment of neonatal thyroid dysfunction is of utmost importance. With advances in neonatal care and increased survival of premature babies we need proper guidelines in NBS of preterm babies. Thyroid dysfunction is a common problem in preterm infants with several risk factors predisposing to it such as immature hypothalamic-pituitary-thyroid axis, impaired synthesis and metabolism of thyroid hormones and increased demand of thyroid hormones due to non-thyroid illness and drug administration. It is still controversial about the timing and optimal treatment of thyroid dysfunction in preterm infants. Adding to it the neurodevelopmental outcome of untreated thyroid dysfunction in preterm infants is still unclear. Preterm infants are more vulnerable if it is small for gestational age. SGA is associated with poor cognitive and sensorimotor functions. Very few studies are there that have studied thyroid function in preterm SGA infants. Hence, we wanted to compare thyroid hormone profile between preterm SGA and AGA and also see if there is any association of demographic factors, clinical conditions and usage of medications with the TFT reports of preterm SGA and AGA infants. Paediatric endocrinologists recommend evaluating both TSH and free thyroxine for newborn screening in preterm neonates. It is considered that primary screening tests and following the tests with both TSH and free thyroxine could diagnose transient hypothyroid dysfunctions including congenital hypothyroidism with delayed TSH elevation. Hence, we tested TSH and FT4 on day of life 4 and repeated screening on day of life 14.

Preterm SGA group had most infants in ELBW group while preterm AGA group had most infants in VLBW group. TSH was significantly high in SGA preterms compared to AGA preterms in all birth weight categories. FT4 was on higher side in AGA preterms in VLBW group and in LBW group whereas it was on higher side in SGA preterm in ELBW. Most of the infants were in very Preterm category (28-32 weeks) in both SGA and AGA group. TSH was significantly higher in SGA preterms compared to AGA preterms in all birth weight categories.
elevated in very preterm and moderate to late preterm groups in SGA preterms compared to AGA preterm. Chunhua et al also got significant TSH elevation in preterm SGA in VLWB Group and mild preterm (GA 32-36 6/7 weeks). We also noted that FT4 increases as gestation increases in both SGA and AGA preterm categories and FT4 was higher in AGA preterm compared to SGA preterms in both very preterm and moderate to late preterm categories. Chun et al observed increasing concentration of T3 and T4 with increasing age. 10 preterms were twins in SGA group and 13 preterms were twins in AGA group. Asper a recent study the incidence of SGA in twin pregnancies is 25-35%. Growth of multiple foetuses in uterus is comparable to growth of singletons in first and second trimester of pregnancy, while it drastically reduces in third trimester due to increased demand for room and nutrients.

The study revealed that SGA preterms have TSH on the higher side within normal limit when compared to AGA preterms while no significant association was obtained for FT4. Radet et al. found that TSH concentrations are significantly higher in children born SGA, and 20% SGA children have TSH levels above the upper limit of the normal range, whereas no difference was found for FT4. De Kort et al. found higher TSH levels within the normal range in preterm short SGA children, but mean FT4 is not significantly different. Chunhua et al found out significant TSH elevation within normal limit in preterm SGA neonates when compared with preterm AGA neonates. Although these findings cannot lend direct support to our conclusion, they distinctly suggest that TSH elevation may play a similar role at different stages of the developmental process.

As thyroid hormones have been credited with a wide range of important physiological functions, the aetiology of higher TSH levels in SGA infants is worth exploring. It is postulated that many factors may involve, including immaturity of the hypothalamic-pituitary-thyroid axis, uterine stress with growth restriction, less efficient thermogenic response, or non-thyroidal illness. However, it is difficult to figure out the temporal pattern of thyroid hormone alteration caused by SGA stunting and to distinguish it from that of AGA infants, as TFT is generally done at separate time periods in various studies. Furthermore, exposure to various medications in hospitalisation and the inability to regulate iodine balance may be other common reasons. Low APGAR at 5 min was seen more in SGA and was noted to be of statistical significance. (p value 0.001) APGAR score at 1 and 5 minutes is a good indicator of perinatal asphyxia. Low APGAR score indicate birth asphyxia and it has been associated with increase TSH levels. Chunhua et al found that perinatal hypoxia was more in preterm SGA compared to preterm AGA neonates. Mode of delivery was evaluated and 23 preterm SGA were born by EMLSCS, 1 by vacuum delivery and rest by vaginal delivery whereas 44 preterm AGA were born by vaginal delivery, 12 by EMLSCS, 2 by ELECTIVE LSCS and 1 by forceps assisted vaginal delivery. Difficult deliveries tend to elevate TSH levels. Emergency caesarean section (done due to prenatal stress) was seen in more in SGA preterms compared to preterm AGA neonates in our study. Chunhua et al noticed higher percentage of LSCS in SGA preterms. However Rashmi et al studied lower TSH levels with elective caesarean section Zung et al in 2017 evaluated mode of deliveries and found out that TSH associated more with caesarean section reflecting some addition of prenatal stress to development of thyroid dysfunction. SGA infants do not have relatively mature functions of organ systems that AGA infants possess, so they are more susceptible to birth asphyxia and difficult deliveries, which tend to elevate TSH levels. There are several studies that shows that thyroid function in preterm are affected by neonatal conditions like respiratory distress syndrome, intraventricular haemorrhage, congenital heart disease, necrotising enterocolitis and usage of medications. Zung et al studied medications like ibuprofen, dopamine, antibiotics were commonly used in neonates with thyroid dysfunction like dTSH. They reflected severity of illness in neonates. Berghe et al showed association of thyroid dysfunction with usage of dopamine suppression of hypothalamo-pituitary-thyroid axis. They also showed association of CHD with thyroid abnormality although specific heart disease was not studied. The present study observed TSH on higher side in AGA preterms with intraventricular haemorrhage (p value 0.003), though we could not find any association...
between clinical conditions such as CHD, necrotising enterocolitis and NICU intervention such as surfactant administration, and use of medications (steroids, dopamine and furosemide) and thyroid hormone profile in preterm SGA and AGA infants. Besides altered thyroid hormone concentrations within normal limit, we studied different kinds of thyroid dysfunction diagnosed by repeat screening during second week of life. Though we did not get any significant association, transient hypothyroidism was seen in 1 SGA preterm and 2 AGA preterms, transient hypothyroxinaemia was seen in 3 SGA preterms and 5 AGA preterms, hyperthyrotropinemia was seen in 4 each in SGA and AGA preterms, and 1 case of delayed TSH elevation in preterm SGA group when no cases were noted in AGA preterm. Yilmas et al in 2021 studied factors associated with THOP and found out that being SGA is 4.6 times increased risk for having thyroid dysfunction. Chunhua et al studied various thyroid dysfunction is preterm SGA and AGA and found significant association for SGA group with dTSH, L-thyroxine therapy and follow up up to 6 months. Our findings further underline preterm SGA infants are prone to thyroid dysfunction and should be closely followed up. Given the importance of proper thyroid function, especially for the overall development and cognitive sequelae, differential effects of preterm and SGA birth on cognitive and motor development have been noted. SGA birth is associated with cognitive ability, as measured by IQ and reading comprehension, while motor ability was additionally associated with preterm birth. Furthermore, Trumpf et al. reported lower verbal IQ scores in preschool children with high TSH values between 10 and 15 mU/L in univariate analysis, but the result did not hold significance after adjusting for confounding factors. Chung et al. suggested TSH level > 10 mU/ml after 2 weeks of life generally abnormal. They confirmed preterm infants with persistently high TSH levels have worsened neurological outcomes compared to those with transiently high TSH levels. In addition, those who had hyperthyrotropinemia and not treated with thyroxine showed poor neurodevelopmental outcome in comparison with those who had normal thyroid function. (p < 0.05). Nonetheless, most of the existing studies have inconclusive results and the clinical significance of neonatal TSH elevation is still under debate. Considering the potential cognitive risks in infancy and childhood, preterm SGA infants with TSH elevation within normal limits should be closely followed up.

LIMITATIONS
Study has several limitations. First, the number of cases is relatively small compared to largescale NBS, and this was a single hospital-based study so it may not reflect the patterns seen in all hospitals. Further studies including more cases are warranted to confirm the findings. Second, the outcomes of babies who got admitted after 1 week of age or those babies who left against medical advice and those who were referred could not be reflected in this study. Third, we were not able to follow up all babies beyond 2 weeks of life. Further followup is required to complete thyroid screening in preterm babies.

CONCLUSION
Preterm SGA newborns had significantly higher TSH concentrations within the normal range and FT4 was on the lower side compared to AGA preterm group. Repeat screening done at day of life 14 showed various thyroid dysfunction in both SGA and AGA preterm groups like transient hypothyroidism, transient hypothyroxinemia, delayed TSH elevation and hyperthyrotropinemia. The present study observed TSH on higher side in SGA preterms with IVH and significantly high in AGA preterms with intraventricular haemorrhage though we could not find any association between clinical conditions such as CHD, necrotising enterocolitis and NICU intervention such as surfactant administration, and use of medications (steroids, dopamine and furosemide) and thyroid hormone profile in preterm SGA and AGA infants. Thus, we advise newborn screening for thyroid abnormalities and repeated follow up for both
preterm SGA and AGA, with special consideration to preterms with comorbidities.

REFERENCES


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