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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 hypothyroxinaemia 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

neonatal demographic and clinical factors were analysed to identify thyroid dysfunction in preterm SGA and AGA infants

Results: Mean value of TSH was measured to be 5.81mU/L in the SGA group whereas it wasrelatively 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. 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, hyperthyrotropinemia 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. 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. It was observed that 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. It was statistically significant with p value 0.003 in AGA group.Clinical conditions like CHD, IVH NEC did not affect FT4 values in preterm SGA andAGA group. 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.

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 bothSGA and AGA preterm groups. Newborn screening for thyroid abnormalities and repeated follow upfor bothpreterm SGA and AGA, with special consideration to preterms with comorbidities is advisable.

Keywords: *Thyroid hormone, Thyroid-stimulating hormone, Small for gestational age, Preterm, Newborn, Thyroid dysfunction, Thyroid Hormone Profile*

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.[1] Several studies suggest that prenatal and early post-natal life are affected by hypothalamo-pituitary-adrenal axis and thyroid function.[2,3]The hypothalamo-pituitarythyroid 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.[4] Untreated congenital hypothyroidism can lead to intellectual disabilities and developmental abnormalities.[5]Even transient hypothyroxinaemia in early neonatal period can cause neurologic and mental problems.[6]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.[5] 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.[7] 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.**2** Further-more, catch up growth during early childhood for SGA infants and its

pattern are influenced by hypothyroidism and LT4 replacement therapy.[8,9]Cianfarani et al found that SGA child with blunted CUG had higher TSH concentration suggesting that thyroid function might affect their postnatal growth.[10]Uchiama et al added that being SGA is a risk factor for transient hypothyroxinaemia with delayed TSH elevation (dTSH) in congenital hypothyroidism in VLBW infants.[11]Further, Chunhua Liu proved that SGA is a risk factor for thyroid dysfunction in preterm newborns.[12]There are very few studies that showed altered thyroid hormones in the first week oflife in preterm SGA, so further studies are required. We did the present study to comparethyroid hormone profile among preterm SGA and preterm AGA and to see if being SGAmakes the preterm babies more susceptible to thyroid dysfunction and if anycomorbidities of the preterm newborns have any association with their thyroid hormoneprofile.

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 1stFebruary 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-inflammatorydrugs/radiation were excludedAfter exclusion, 148 preterm infants (74 SGA and 74 AGA infants) entered into the finalanalysis.The Thyroid function test was performed on Day 4 of life in preterm SGA andpretermAGA infants in NICU and repeated on Day 14.3ml venous blood sample was drawn into sterilevacutainers 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 structuredProforma by interviewing mother.The neonatal demographic characteristics included sex,birth weight, gestation, being atwin and mode of delivery.The history of clinical conditionssuch as 5- min Apgar scores, presence of respiratorydistress syndrome detected byadministration of surfactant, severe intraventricularhaemorrhage defined as grade III/IV,necrotising enterocolitis provenclinically/radiologically, and cardiac problems proven by 2decho report, and NICUintervention such as surfactant administration, and use of medications(steroids,dopamine and furosemide), were collected.Thyroid dysfunction is assessed basedon standard reference ranges for pretermneonates based on gestation and day of sampling.

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

Transient hypothyroxinemia is defined as low FT4 with normal or low TSHnormalized in subsequent screening

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

Hyperthyrotropinemia is defined as TSH elevation with normal or elevated FT4 thatreverts to normal in subsequent screening

The data was entered in MS EXCEL spreadsheet. The data was analysed usingSPSS version20. Comparison was made between AGA and SGA Preterm thyroidfunction test results andunpaired 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 forgestational age whereas 74 were small for gestational age.It was observed that among the study participants,in preterm SGA group 64.86% weremales and 35.13% were female patients while in preterm AGA group 43.24% weremales and 56.75% were female patients. Twin pregnancy was observed in 13.51% inpreterm SGA group and 12.16% in

preterm AGA group.Mode of delivery was analysed and it was found that in preterm SGA group 24.32%were delivered byEMLSCS, 2.7% by vacuum assisted vaginal delivery and 72.97% bynormal vaginal delivery whereas in preterm AGA group 27.03% were delivered byEMLSCS, 2.7% by electiveLSCS, 2.7% by forceps assisted vaginal delivery and67.56% by normal vaginal delivery.The mean birth weight of SGA group was found to be 1.0369±0.241 and 1.21±0.26kgin 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 majoritybelonged toVLBW 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 wasrelatively less in the AGA group with mean value of 4.42 mU/L. The p value was<0.0001which was found to be statistically significant. Mean FT4 value in SGApreterms was 1.69ng/dl while in AGA preterms was 1.97ng/dl. (Table 1)

TABLE 1: Comparison of mean TFT between SGA and AGA preterm groups

TFT	SGA (n 74)	AGA (n 74)	P value
TSH(mU/L) (presented as mean and standard deviation	5.81± 1.54	4.42± 1.44	<0.0001
FT4 (ng/dl) presented as mean and standard deviation	1.69± 0.34	1.97± 0.5	0.43

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, hyperthyrotropinemia 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 2: Distribution of thyroid dysfunction in SGA and AGA preterms based on repeat screening

Thyroid dysfunction	SGA(Frequency)	AGA(Frequency)	P value
Transient Hypothyroidism	1	2	0.64
Transient hypothyroxinaemia	3	5	0.45
dTSH	1	0	-
Hyperthyrotropinemia	4	4	0.44

In the study low APGAR score at 5 minute (score <7) was seen in 18.91% in SGA preterms and8.1% in AGA preterms.We observed statistically significant higher TSH (7.46±0.66) inlow APGAR preterm SGA babies and statistically significant higher TSH (7.74±1.22)in low APGAR preterm AGA babies. (Table 3)

TABLE 3: Comparison of TSH between low APGAR score and normal APGAR score group in SGA and AGA preterms

APGAR score	AGA preterm TSH (mean±SD)	SGA Preterm TSH (mean±SD)
Low	7.74 ±1.22	7.46±0.66
Normal	4.12 ±1.02	5.42 ±1.43
P value	<0.001	<0.001

Table 4 shows that 18.91% SGA preterm and 29.72% of AGA preterms hadcongenital heart disease, 10.81% SGA preterm and 2.7% of AGA preterms had severeintraventricular haemorrhage and 9.5% SGA preterm and 5.4% of AGA preterms hadnecrotising enterocolitis.

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

Clinical conditions	SGA Frequency (Percentage)	AGA Frequency (Percentage)
CHD	14(18.91%)	2(29.72)
IVH	8(10.81%)	2(2.7%)
NEC	7(9.5%)	4(5.4%)
Surfactant administration	8(10.81%)	18(24.32%)
Steroids	4(5.4%)	6(8%)
Dopamine	2(2.7%)	2(2.7%)
Furosemide	4(5.4%)	2(2.7%)

TSH was on higher side in severeintraventricular haemorrhage (6.65±1.8) in preterm SGA group and (6.65±1.8) inpretermAGA group. (p value 0.003 in AGA group.) Clinical conditions like CHD, IVH, NEC did not affect FT4 values in preterm SGA andAGA group.10.81% SGA preterm and 24.42% of AGA pretermsrequired 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 and2.7% of AGA pretermsused furosemide.(Table 4)Medications like surfactant administration,usage of steroids, dopamine and furosemide did not affect TSH and FT4 concentrationin preterm SGA and AGA in the present study.

DISCUSSION

Normal development of brain requires proper thyroid functioning, especially in the firsttwoyears postnatally. Therefore, early identification and proper treatment of neonatalthyroid dysfunction is of utmost importance. With advances in neonatal care andincreased survival of premature babies we need proper guidelines in NBS of pretermbabies. Thyroid dysfunction is a common problem in preterm infants with several riskfactors predisposing to it such as immature hypothalamic-pituitary-thyroid axis,impaired synthesis and metabolism of thyroid hormones and increased demand ofthyroid hormones due to non-thyroid illness and drug administration.[17-18]It is stillcontroversial about the timing and optimal treatment of thyroid dysfunction inpremature infants. Adding to it the neurodevelopmental outcome of untreated thyroiddysfunction in preterm infants is still unclear. Preterm infants are more vulnerable ifits small for gestational age. SGA is associated with poor cognitive and sensorimotorfunctions. Very few studies are there that have studied thyroid function in preterm SGAinfants. Hence, we wanted to compare thyroid hormone profile between preterm SGAand AGA and also see if there is any association of demographic factors, clinicalconditions and usage of medications with the TFT reports of preterm SGA and AGAinfants. Paediatric endocrinologists recommend evaluating both TSH and freethyroxine for newborn screening in preterm neonates.[19]It is considered that primaryscreening tests and following the tests with both TSH and free thyroxine could diagnosetransient hypothyroid dysfunctions including congenital hypothyroidism with delayedTSH elevation. Hence, we tested TSH and FT4 on day of life 4 and repeated screeningon day of life 14.

Preterm SGA group hadmost infants in ELBW group while preterm AGA group had most infants in VLBWgroup. TSH was significantly high in SGA preterms compared to AGA preterms in allbirth weight categories. FT4 was on higher side in AGA preterms in VLBW group andLBW group whereas it was on higher side in SGA preterm in ELBW. Most of theinfants were in very Preterm category (28-32 weeks) in both SGA and AGA group.TSH was significantly

elevated in very preterm and moderate to late preterm groups inSGA preterms compared to AGA preterm. **Chunhua et al** also got significant TSHelevation in preterm SGA in VLBW Group and mild preterm (GA 32-36 6/7 weeks).[12]We also noted that FT4 increases as gestation increases in both SGA and AGA pretermcategories and FT4 was higher in AGA preterm compared to SGA preterms in bothvery preterm and moderate to late preterm categories. **Chun et al** observed increasingconcentration of T3 and T4 with increasing age.[25]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%.[20]Growth ofmultiple foetuses in uterus is comparable to growth of singletons in first and secondtrimester of pregnancy, while it drastically reduces in third trimester due to increaseddemand for room and nutrients.

The study revealed that SGA preterms have TSH on the higher side within normal limitwhen compared to AGA preterms while no significant association was obtained forFT4. **Radet et al.** found that TSH concentrations are significantly higher in childrenborn SGA, and 20% SGA children have TSH levels above the upper limit of the normalrange, whereas no difference was found for FT4.[21] De Kort et al. found higher TSHlevels within the normal range in preterm short SGA children, but mean FT4 is notsignificantly different.[22] Chunhua et al found out significant TSH elevation withinnormal limit in preterm SGA neonates when compared with preterm AGA neonates.[12]Although these findings cannot lend direct support to our conclusion, they distinctlysuggest that TSH elevation may play a similar role at different stages of thedevelopmental process.

As thyroid hormones have been credited with a wide range of important physiologicfunctions,the aetiology of higher TSH levels in SGA infants is worth exploring. It ispostulated that manyfactors may involve, including immaturity of the hypothalamic-pituitary-thyroid axis, uterine stress with growth restriction, less efficient thermogenicresponse, or non-thyroidal illness.However, it is difficult to figure out the temporalpattern of thyroid hormone alteration caused by SGA stunting and to distinguish it fromthat of AGA infants, as TFT is generally done at separate time periods in variousstudies. Furthermore, exposure to various medications in hospitalisation and theinability 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 statisticalsignificance. (p value 0.001) APGAR score at 1 and 5 minutes is a good indicator ofperinatal asphyxia. Low APGAR score indicate birth asphyxia and it has beenassociated with increase TSH levels Chunhua et al found that perinatal hypoxiawas more in preterm SGA compared topreterm AGA neonates.[12]Mode of delivery was evaluated and 23 preterm SGA were born by EMLSCS, 1 byvacuum delivery and rest by vaginal delivery whereas 44 preterm AGA were born byvaginal delivery, 12 by EMLSCS, 2 by ELECTIVE LSCS and 1 by forceps assistedvaginal delivery. Difficult deliveries tend to elevate TSH levels. Emergency caesareansection(done due to prenatal stress) was seen in more in SGA preterms compared topreterm AGAneonates in our study. Chunhua et al noticed higher percentage of LSCSin SGA preterms.[12]However Rashmi et al studied lower TSH levels with electivecaesarean section Zung et al in 2017 evaluated mode of deliveries and found out thatdTSH associated more withcaesarean section reflecting some addition of prenatal stressto development of thyroid dysfunction.[17]SGA infants do not have relatively maturefunctions of organ systems that AGA infants possess, so they are more suspectable tobirth asphyxia and difficult deliveries, which tend to elevate TSH levels. There are several studies that shows that thyroid function in preterm are affected byneonatal conditions like respiratory distress syndrome, intraventricular haemorrhage,congenital heart disease, necrotising enterocolitis and usage of medications.[14-15]Zunget al studied medications like ibuprofen, dopamine, antibiotics were commonly used inneonates with thyroid dysfunction like dTSH. They reflected severity of illness inneonates.[17] Berghe et al showed association of thyroid dysfunction with usage ofdopamineby suppression of hypothalamo-pituitary-thyroid axis. They also showedassociation of CHD with thyroid abnormality although specific heart disease was notstudied.[16]

The present study observed TSH on higher side in AGA preterms with intraventricularhaemorrhage (p value 0.003), though we could not find any association

between clinicalconditions such as CHD, necrotising enterocolitis and NICU intervention such assurfactantadministration, 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 studieddifferent kinds of thyroid dysfunction diagnosed by repeat screening during secondweek of life. Though we did not get any significant association, transienthypothyroidism was seen in 1 SGA preterm and 2 AGA preterms, transienthypothyroxinaemia was seen in 3 SGA preterms and 5 AGA preterms,hyperthyrotropinemia was seen in 4 each in SGA and AGA preterms and 1 case ofdelayed TSH elevation in preterm SGA group when no cases were noted in AGApreterm. Yilmas et al in 2021 studied factors associated with THOP and found out thatbeing SGA is 4.6 timesincreased risk for having thyroid dysnfunction.[23] Chunhua etal studied various thyroid dysfunction is preterm SGA and AGA and found significantassociation for SGA group with dTSH, L-thyroxine therapy and follow up upto 6months.[12]Our findings further underline preterm SGA infants are prone to thyroiddysfunction and should be closely followed up.Giventhe importance of proper thyroid function, especially for the overall developmentin early andlater childhood, some cohort studies investigated the impact of highneonatal TSH levels onlong-term developmental and cognitive sequelae. Differentialeffects 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 readingcomprehension, while motor ability was additionally associated with preterm birth.Furthermore, Trumpff et al. reported lower verbal IQ scoresin preschool children withhigh TSH values between 10 and 15 mU/L in univariate analysis, but the result did nothold significance after adjusting for confounding factors [24]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 worseneurological outcomes compared to those with transiently high TSH levels. In addition,those who had hyperthyrotropinemia and not treated with thyroxine showed poorneurodevelopmental outcome in comparison with those who had normal thyroidfunction. ($p < 0.05$)[25]Nonetheless, most of the existing studies have inconclusive results and the clinicalsignificance of neonatal TSH elevation is still under debate. Considering the potentialcognitive risks in infancy and childhood, preterm SGA infants with TSH elevationwithin 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 wasa single hospital-based study so it may not reflect the patterns seen in all hospitals.Further studies including more cases are warranted to confirm thefindings.Second, the outcomes of babies who got admitted after 1 week of age or those babieswho left against medical advice and those who were referred could not be reflected inthis 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 concentrationswithin the normal range and FT4 was on the lower side compared to AGA pretermgroup.

Repeat screening done at day of life 14 showed various thyroid dysfunction in bothSGA and AGA preterm groups like transient hypothyroidism, transienthypothyroxinemia, delayed TSH elevation and hyperthyrotropinemia.

The present study observed TSH on higher side in SGA preterms with IVH and significantly highin AGA preterms with intraventricular haemorrhage though we could not find anyassociation between clinical conditions such as CHD, necrotising enterocolitis andNICUintervention such as surfactant administration, and use of medications (steroids,dopamine and furosemide) and thyroid hormone profile in preterm SGA and AGAinfants.

Thus,we advise newborn screening for thyroid abnormalities and repeated follow upfor both

preterm SGA and AGA, with special consideration to preterms withcomorbidities.

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