

## A Cross Sectional Study of Thyroid Hormone Profile in Low Birth Weight As Compared To Term Appropriate for Gestational Age Newborn In A Tertiary Care Rural Based Hospital

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**Abstract:** The signs and symptoms of congenital hypothyroidism are often not easily recognizable and newborns should be screened soon after birth for early detection. India accounts more than 40% of the global burden of low birth weight babies. Small-for-gestational-age are more prone for development of thyroid disorders which may affect neonatal adaptation and future health in infancy and adulthood. Preterm babies have immature hypothalamic-pituitary-thyroidal axis, synthesis and metabolism with systemic disease and exposure to drugs which make them more susceptible to have abnormal thyroid profile. The study is aimed to estimate and compare thyroid profile between preterm / term SGA babies and normal birth weight babies. 90 newborns comprising of three groups including preterm AGA, term SGA, term AGA were screened for thyroid hormones (T<sub>3</sub>, T<sub>4</sub>, TSH) between day 3 and day 7 of life with venous blood sample. Both Preterm AGA and term SGA babies have significant thyroid profile abnormality compared to term AGA newborns with lower T<sub>3</sub>, T<sub>4</sub> and higher TSH levels than term AGA (p value < 0.05)

### I. Introduction

Thyroid hormones are required for growth and neurocognitive development. As the signs and symptoms of congenital hypothyroidism are often scarce and not easily recognizable, newborns should be screened soon after birth for early detection. Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation. Excellent outcome is seen in infants with congenital hypothyroidism those who are diagnosed and treated early, in terms of normal mental and neurologic performance. It is seen physical recovery is good and stature is normal, when replacement therapy is begun within the first 2 months of life. If treated early the babies have IQ > 85 and if left untreated babies develop impairment in visuospatial processing, arithmetic ability, speech, or fine motor coordination, selective memory and sensorimotor defects.<sup>1</sup>

India accounts more than 40% of the global burden of low birth weight babies with 7.5 million babies (or 30% of the country's total annual live births) being born with a birth weight less than 2500 grams. Of these 7.5 million babies, 60% are born at term after fetal growth restriction, while the remaining 40% are born preterm, constituting a quarter of the global burden of preterm births (INAP). Babies with a birth weight and/or length below the 10th percentile of a population of the same gestational age are defined small-for-gestational-age (SGA).<sup>2</sup> IUGR results due to complex factors of fetal, placental and maternal origin.<sup>3,4</sup> and it leads to a state of chronic fetal stress. Due to these alterations SGA neonates are more prone for development of thyroid disorders which may affect neonatal adaptation and future health in infancy and adulthood: indeed, higher incidences of pathologies such as cardiovascular events, metabolic syndrome, hypertension and obesity have been demonstrated.<sup>5</sup>

Preterm infants have immaturity of the hypothalamic-pituitary-thyroid axis, immature thyroid hormone synthesis, immature thyroid hormone metabolism, and systemic diseases in addition to insufficient or excessive iodine intakes and other drugs which influence preterm thyroid function.

### II. Materials And Methods

This study was conducted in Bankura Sammilani Medical College at the Neonatal care unit of Pediatric Department and Postnatal care ward of Gynecology and Obstetric Department. It was conducted for a period of 1 year from 2015 to 2016, on 90 newborns which comprised three groups including preterm AGA, term SGA, term AGA of 30 newborns in each group. They were screened for thyroid hormones (T<sub>3</sub>, T<sub>4</sub>, TSH) between day 3 and day 7 of life. Venous blood sample was collected and analysed with Mindray microplate ELISA reader. Thyroid hormone profile of all the three groups was studied and that of preterm AGA and term SGA was compared with term AGA. Abnormal thyroid profile is considered when either T<sub>4</sub> is less than 6.5 ug/dl and TSH is more than 20 uIU/ml or both T<sub>4</sub> is less than 6.5 ug/dl and TSH more than 20 uIU/ml.<sup>6</sup>

**Statistical Analysis:**

SAMPLE SIZE was calculated as per the formula  $N(\text{for each group}) = [(z_{\alpha} + z_{\beta})^2 (s_1^2 + s_2^2)] / d^2$ , where the  $z_{\alpha} = 1.96$  at 5% precision considering two tail test &  $z_{\beta} = 0.84$  with 80% power of the test;  $s_1$  &  $s_2$  are the standard deviations of serum TSH level among the preterm and term babies (as stated in the earlier studies)<sup>7,8</sup>,  $d$  = difference between the mean serum TSH level of the two groups i.e. preterm & term newborn. Statistical methods (mean, standard deviation) and IBM SPSS 20.0 software was used to analyse the data. Study of significance was analysed by Chi square test for qualitative data and ANOVA test for quantitative data. P value <0.05 is considered significant.

**III. Result And Analysis**

The mean gestational of population we studied was 33.4 weeks in preterm, 38.6 weeks in term SGA and 38.86 weeks in term AGA and the mean birth weight of preterm babies is 1.76kg, term SGA babies is 2.04kg and term AGA babies is 2.723kg. In our present study total of 18 newborns had abnormal thyroid profile out of which 6 (33.33%) had normal T<sub>4</sub>, high TSH; 9 (50.00%) had low T<sub>4</sub>, normal TSH and 3 (16.66% ) had low T<sub>4</sub>, high TSH. Ten out of 45 boys (24.44%) and seven out of 45 girls (15.55%) found to have thyroid dysfunction in neonates. So frequency was higher among boys. Thyroid dysfunction was higher in tribal population 37.5% (6 out of 16) than the non tribal population 16.21% (12 out of 74).

In our study also abnormal thyroid profile present in 30% preterm AGA with 23.33% (7 out of 30) had only low T<sub>4</sub> and 6.67% (2 out of 30) had both elevated TSH and low T<sub>4</sub>. In term SGA abnormal thyroid profile is seen in 26.67 newborns with 3.33% (1 out of 30) had both elevated TSH and low T<sub>4</sub>, 6.67% (2 out of 30) had only low T<sub>4</sub>, 16.67 (5 out of 30) had only elevated TSH. In case of term AGA only 3.33% (1 out of 30) had normal T<sub>4</sub> and raised TSH.

Neonates	Low T <sub>4</sub> , High TSH	Low T <sub>4</sub> , Normal TSH	Normal T <sub>4</sub> , High TSH	Normal T <sub>4</sub> , Normal TSH	Total
Preterm AGA	2(6.67%)	7(23.33%)	0	21	30
Term SGA	1(3.33%)	2(6.67%)	5 (16.67%)	22	30
Term AGA	0	0	1 (3.33%)	29	30
<b>Total</b>	<b>3</b>	<b>9</b>		<b>72</b>	<b>90</b>

**Table-1:** Abnormal thyroid profile in term SGA as compared to term AGA

Thyroid Profile	Abnormal Thyroid Profile	Normal T <sub>4</sub> , Normal TSH	Total	P value Fisher's exact test	OR (95% CI)
Term SGA	8	22	30	<b>0.026</b>	<b>0.095(0.011-0.815)</b>
Term AGA	1	29	30		
<b>Total</b>	<b>9</b>	<b>51</b>	<b>60</b>	-----	-----

Abnormal thyroid profile in Term SGA is significantly more than Term AGA with a p value less than 0.05

**Table- 2:** Abnormal thyroid profile in preterm AGA as compared to term AGA

Thyroid Profile	Abnormal Thyroid Profile	Normal T <sub>4</sub> , Normal TSH	Total	χ <sup>2</sup> , df, P value Pearson Chi-Square	OR (95% CI)
Preterm AGA	9	21	30	<b>7.68, 1, 0.006</b>	<b>0.08(0.009-0.685)</b>
Term AGA	1	29	30		
<b>Total</b>	<b>10</b>	<b>50</b>	<b>60</b>	-----	-----

Abnormal thyroid profile in Preterm AGA is significantly more than Term AGA with a p value of less than 0.05.

Mean T<sub>3</sub>, mean T<sub>4</sub> of preterm AGA are significantly less than that of Term AGA with p value less than 0.05 and mean TSH of Preterm AGA is significantly more than that of Term AGA with p value is less than 0.05 for TSH

	Preterm AGA	Term AGA	Pvalue (ANOVA)
Mean T <sub>3</sub>	90.27	134.9	<0.001
Mean T <sub>4</sub>	7.20	9.50	<0.001
Mean TSH	10.83	6.93	0.032

Mean T<sub>3</sub> and mean T<sub>4</sub> of Term SGA is significantly less than that of Term AGA and mean TSH of Term SGA is significantly more than Term AGA with p value less than 0.05.

	<b>Term SGA</b>	<b>Term AGA</b>	<b>Pvalue (ANOVA)</b>
Mean T <sub>3</sub>	121.7	134.9	0.002
Mean T <sub>4</sub>	8.43	9.50	0.009
Mean TSH	13.73	6.93	0.000

#### IV. Discussion

In SGA newborns the role of hormones such as insulin, glucagon, cortisol, ACTH and GH have been studied in depth extensively upto infancy.<sup>9-12</sup> However in the neonatal period secretion of thyroid hormones in SGA subjects has been less investigated. Only eight published studies have examined differences in secretion of thyroid hormones in AGA and SGA babies in the fetal period or the first week of life. One analyzed these hormones by cordocentesis in the fetal period, four in cord blood at birth and two in the first week of life and subsequent days.<sup>13-18</sup>

Our results conform with those of Setia et al.<sup>13</sup> or Padwal et al.<sup>19</sup> who studied cord blood and those of Thorpe-Beeston et al.<sup>14</sup> who used cordocentesis, all finding higher concentrations of TSH and lower concentrations of T<sub>4</sub> in SGA newborns. It is also consistent with works of Bagnoli et al, where samples were taken from newborns on third day of life depicting increased TSH with decreased T<sub>4</sub> in SGA newborns.<sup>3</sup> Our results are in contrast with those of Nieto-Diaz et al.<sup>17</sup> and Brock Jacobsen et al.<sup>18</sup> so far as TSH concentrations are concerned. However, Rashimi et al.<sup>16</sup> and Mahajan et al.<sup>15</sup> estimated cord blood plasma concentrations of thyroid hormones and did not find any significant difference between SGA and AGA newborns.

We assessed babies between the third and seventh day of life. It is expected that our results would not be affected by confounding factors such as type of delivery, fetal distress and maternal diseases, all of which may affect TSH secretion at birth. Our finding of higher TSH and lower T<sub>4</sub> in SGA newborns indicates reduced fetal secretion of T<sub>4</sub> persisting in the first days after delivery. This reduced secretion could be due to retarded development of the gland, caused by the malnutrition typical of intrauterine growth retardation, and by associated placental hypoxia.

Of the available studies evaluating thyroid hormone profile, sampling of blood from newborn in the first week of life was done only by Bagnoli et al and our results were comparable with them. Other researchers drew blood sample from cord either in intrauterine period or soon after birth. Our data cannot be compared with that of Brock Jacobsen et al<sup>18</sup>, who examined babies after the first week of life. Also, it is not comparable with works sampling cord blood, where stress factors operate. Since differences in TSH between AGA and SGA babies are relatively small and can only emerge in a large population, the population examined by Nieto-Diaz et al<sup>17</sup> was presumably too small to detect statistically significant differences. Our finding of higher TSH and lower T<sub>4</sub> in SGA newborns indicates reduced fetal secretion of T<sub>4</sub> persisting in the first days after delivery. This reduced secretion could be due to retarded development of the gland, caused by the malnutrition typical of intrauterine growth retardation, and by any placental hypoxia.

The incidence of abnormal thyroid profile in preterm infants was high in this study. Thyroid hormone is associated with the neurodevelopment of preterm infants.<sup>20,21</sup> Despite many studies on thyroid function in preterm infants, its significance is still debated. Moreover, there has been much debate about the need for routine repeat thyroid function tests for preterm infants<sup>22,23</sup> and thyroid hormone replacement in hypothyroxinemia of prematurity.

In term neonates, blood specimens are used to measure TSH levels and screen for congenital hypothyroidism during the first 2 to 5 days of postnatal life. However, the TSH surge and pituitary feedback for thyroid hormone are limited and TSH may not be increased even though serum thyroid hormone is low in preterm infants.<sup>24</sup> In addition, very low birth weight infants usually have various systemic diseases and are given various drugs such as dopamine, dobutamine and morphine that affect the hypothalamic-pituitary-thyroidal axis. Thus, TSH levels are not representative of overall thyroid function in preterm infants. This study was conducted in stable newborns between third and seventh day of life to eliminate stress and/or drug induced alteration thyroid hormone level.

Fisher et al<sup>8</sup> Ares et al<sup>25</sup> stated that in the preterm infant, there is a similar TSH, T<sub>4</sub>, and T<sub>3</sub> surge, but the magnitude is attenuated. In babies born at more than 30 weeks gestation, T<sub>4</sub> and free T<sub>4</sub> levels increase over the next six to eight weeks to levels comparable to those of babies born at term. Ares et al<sup>3</sup>, Rooman et al<sup>151</sup>, Frank et al<sup>24</sup>, Van Wassenaer et al<sup>26</sup> mentioned that however, in the preterm baby born at less than 30 weeks gestation and with very low birth weight (< 1500 g), the TSH and T<sub>4</sub> surges are limited and there is often a fall in T<sub>4</sub> in the first one to two weeks after birth, and transient hypothyroxinemia is common. Our study is also in line with the above mentioned studies and shows that T<sub>3</sub>, T<sub>4</sub>, are less in preterm AGA as compared to term AGA babies. However TSH was significantly elevated in preterm AGA compared to term AGA.

Chung et al<sup>7</sup> stated that there is higher incidence of thyroid dysfunction in preterm infants with 30% having only low T<sub>4</sub> and 12% having both elevated TSH and low T<sub>4</sub>. In our study also abnormal thyroid profile present in 30% preterm AGA with 23.33% (7 out of 30) had only low T<sub>4</sub> and 6.67% (2 out of 30) had both elevated TSH and low T<sub>4</sub>.

The postnatal thyroid function of preterm infants differs from that of term infants. Blunted postnatal thyrotropin (TSH) surges and low serum T<sub>4</sub> levels are frequently observed in preterm neonates; which is generally referred to as hypothyroxinemia of prematurity. The main factors that influence thyroid function in preterm infants are immaturity of the hypothalamic-pituitary-thyroid axis, immature thyroid hormone synthesis, immature thyroid hormone metabolism, and systemic diseases. Insufficient or excessive iodine intakes also influence preterm thyroid function. However, the TSH surge and pituitary feedback for thyroid hormone are limited and TSH may not be increased even though serum thyroid hormone is low in preterm infants. Hence there is a need for repeat thyroid screening for preterm neonates.

## V. Conclusion

The incidence of abnormal thyroid profile was higher in boy baby compared to girl baby. Tribal population in our study had higher incidence abnormal thyroid profile compared to non tribal population. We observe that the findings T<sub>3</sub>, T<sub>4</sub>, TSH values in preterm and term SGA significantly varies than term AGA. Preterm babies have more incidence of low T<sub>4</sub> and normal TSH indicating hypothyroxinemia. Term SGA babies have predominantly normal T<sub>4</sub> with high TSH indicating thyroid hypofunction. No clinical features of overt hypothyroidism were found in the newborns with abnormal thyroid profile. Hypothyroxinemia in preterm babies require proper follow up and may be given therapeutic support for neurocognitive development. Thyroid hypofunction in SGA babies also need proper follow up of growth, development and thyroid profile assessment. Preterm and SGA babies are at risk for thyroid dysfunction in 1<sup>st</sup> week. Timely institution of treatment for thyroid hypofunction in early infancy is needed.

### Contribution:

Dr. Pal actually planned and conducted the study under the guidance and supervision of Prof. Basu. Dr. Pal also performed the statistical analysis.

Prof. Basu drafted the final manuscript and added important intellectual contents.

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