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Original Research Article

Derangements of Thyroid Hormones and Hypothalmo-Pitutary-Thyroid (HPT) Axis in Preterm Neonates

Dr. Sunita Yadav[1], Dr. Rupita Kulshrestha[2*], Dr. Manish Raj Kulshrestha[3], Dr. Rakesh Kumar Kalra[4]

[1]Consultant Pathologist, Midland Healthcare and Research Centre, Lucknow Uttar Pradesh India
[2]Assistant Professor, Department of Obstetrics and Gynecology Mayo Institute of Medical Sciences, Barabanki Uttar Pradesh India
[3]Associate Professor Department of Biochemistry, Dr. Ram Manohar Lohia Institute of Medical Sciences, Lucknow Uttar Pradesh India
[4]Associate Professor, Department of Pediatrics, N. C. Medical College, Israna Panipat, Haryana India

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***Corresponding author:** Dr. Rupita Kulshrestha

Abstract

Introduction: Preterm neonates have deranged thyroid hormones levels often characterized by low T_3/FT_3 and often low to normal T_4/FT_4 and TSH levels. Thus, it may be essential to find the pattern of thyroid hormones levels in preterm in comparison to term neonates, the status of HPT axis in preterms and occurrence of Transient Hypothyroxinemia of Prematurity (THOP) in this part of globe, since serum FT_3 and FT_4 levels are correlated with TSH levels after establishment of HPT axis. We have focussed on these hormones in our study. ***Methods:*** This prospective observational study was conducted at a tertiary care centre in Northern India including 100 neonates in the study group (33 preterm and 67 term neonates as per gestational age). FT_3, FT_4 and TSH were estimated by electrochemiluminescence immunoassay (ECLIA) using diagnostic kits from Roche Diagnostics. The history of maternal illness, gestational age and birth weight of each neonate was recorded. ***Results:*** All the three hormones i.e. FT_3, FT_4 and TSH were significantly lower in preterm in comparison to term neonates. In term neonates FT_3 was significantly correlated to both FT_4 (r=0.453; p=0.00) and TSH (r=0.299; p=0.014) while no such correlation was found in preterm neonates. ***Discussion:*** Both sick euthyroid (low T_3 syndrome) and transient hypothyroxinemia of premature infants (THOP) are noticed in pereterm neonates. The causes of low T_3 syndrome may include hypoxemia, acidosis, infections, hypoglycemia, hypocalcemia, malnutrition, transient secondary/tertiary hypothyroidism, transient primary hypothyroidism and permanent primary hypothyroidism while THOP may be caused by iodine deficiency, maternal thyrotropin receptor blocking antibodies, maternal intake of anti-thyroid drugs, maternal or neonatal iodine exposure, loss of function mutations and hepatic haemangioma(20), maternal hyperthyroidism, prematurity and drugs. Since it may lead to undesirable neurodevelopmental outcome, thyroid hormones supplementation in preterms should be cautiously studied in larger sample size. Also, these factors must be considered while screening for congenital hypothyroidism.

Keywords: Triiodothyronine (T_3), Tretraiodothyronine (T_4), thyroid stimulating hormone (TSH), Transient Hypothyroxinemia of prematurity (THOP), Hypothalamo-Pituitary-Thyroid axis (HPT) axis.

INTRODUCTION

The progressive major advances during the past few decades in the management of premature neonates has caused significant reduction in their mortality and more than 50% of neonates less than 24 weeks gestation age (GA) now survive, increasing the numbers of VLBW (VLBW, <1500 grams and <30 weeks GA) neonates in nursery intensive care units[1].

Thyroid gland function develops and matures during fetal life, with production of serum thyroxine (T_4) beginning around 12 week's gestation and increasing to term [2]. As compared to term neonates, preterm neonates experience a fall in serum T_4 and T_3 levels to below birth levels in first week of life. This fall appears to be the result of many factors, like nutritional challenges and decreased hepatic Thyroid Binding Globulin (TBG) production, immaturity of hypothalamic-pituitary-thyroid (HPT) axis, and immaturity of the thyroid tissues itself, and increased tissue utilization of T_4. These changes are further influenced by complications of prematurity, such as respiratory distress syndrome (RDS), sepsis, and intraventricular hemorrhages etc. which result in nonthyroidal illness-like changes [3].

Thyroid hormones play a critical role in central nervous system development and function, and thyroid

system immaturities as well as morbidity-related thyroid dysfunction (the nonthyroidal illness syndrome) contribute to the transient hypothyroxinemia of premature infants (THOP)[4,5]. Transient hypothyroxinemia is the commonest thyroid dysfunction in preterm infants and is characterized by temporary postnatal reductions in whole blood levels of T_4 [6] or sera free T_4 (FT_4) [7] but with normal levels of TSH [6, 8]. Transient hypothyroxinemia was previously thought to be without clinical significance [6, 8], but recent studies have found adverse associations between THOP and neurodevelopment [9-12], and low postnatal levels of T_3 and neurodevelopment [13].

Thus, it may be essential to characterize how thyroid hormones levels are different in preterms in comaprison to term neonates, the status of HPT axis in preterms and occurrence of THOP in this part of globe. Since serum FT_3 and FT_4 levels are correlated with TSH levels after establishment of HPT axis. We have focussed on these hormones in our study.

MATERIALS AND METHODS

This prospective observational study was conducted at a tertiary care centre in northern India including 100 neonates in the study as 21 with very low birth weight (VLBW; <1500gms), 23 with low birth weight (LBW; <2500 gms) and 56 with normal birth weight (>2500 gms).

After taking an informed consent from the parent/ guardian, 2ml of venous blood sample was collected from all neonates after 72 hours of life in a sterile vacutainer.FT_4, FT_3 and TSH were estimated by electrochemiluminescence immunoassay (ECLIA) using diagnostic kits from Roche Diagnostics. The neonates were categorized in two groups based on their gestational age. Those born≥ 37 weeks were categorized as term neonates while those ≤ 37 weeks as preterm neonates. The history of maternal illness, gestational age and birth weight of each neonate was recorded. As per gestational age (GA) there were 33 preterm and 67 term neonates in the study group.

RESULTS

We observed 33 preterm and 67 term neonates in our study group. Out of 33 preterm, there were 19 males and 14 females while out of the 67 term neonates, there were 41 males and 26 females.

On categorization of neonates on the basis of GA, it was found that all the three hormones i.e. FT_3, FT_4 and TSH was significantly lower in preterm in comparison to term neonates (Table 1).

The FT_3 in very low birth weight (VLBW) neonates was significantly lower than low birth weight (LBW) babies (p=0.038) and normal birth weight babies (p<0.001). FT_4 and TSH were also being lowest in VLBW and highest in neonates with normal birth weight (BW) but none of these differences were statistically significant (Table 2).

In term neonates FT_3 was significantly correlated to both FT_4 (r=0.453; p=0.00) and TSH (r=0.299; p=0.014) while no such correlation was found in preterm neonates suggesting better development of HPT axis in term neonates than in preterm neonates.

Table-1: A comparison of FT_3, FT_4 and TSH among preterm and term neonates

	Preterm neonates (n=33)	Term neonates (n=67)	p Value
FT_3 (pg/ml) (Mean±S.D.)	3.44 ± 1.06	4.47 ± 1.44	<0.001*
FT_4 (ng/dl) (Mean±S.D.)	21.08 ± 5.44	25.66 ± 6.7	0.049
TSH (µIU/ml) **(Mean±S.D.)**	3.31 ± 2.14	6.10 ± 3.37	0.042

**P value <0.05i.e.the FT_3 of was significantly lower in preterm neonates in comparison to term neonates*

Table-2: A comparison of FT_3, FT_4 and TSH among VLBW, LBW and normal birth weight neonates

	n	VLBW (n=21)	LBW (n=23)	Normal BW (n=56)
FT_3 (Mean±S.D.)	21	3.13 ± 0.99*	4.11 ± 1.09	4.51 ± 1.48
FT_4(Mean±S.D.)	23	19.15 ± 3.77	22.76 ± 5.29	24.20 ± 7.10
TSH(Mean±S.D.)	56	3.16 ± 2.35	4.66 ± 2.96	4.96 ± 3.45

**P value <0.05i.e.the FT_3 of was significantly lower in VLBW neonates in comparison to LBW neonates and the normal BW neonates*

DISCUSSION

The FT_3, FT_4 and TSH levels in preterm were significantly low in comparison to term neonates in our study population similar to findings by Dilli D *et al*. [14] Zhu L *et al*. defined reference intervals of FT_3, FT_4 and TSH for preterm infants according to their gestational age but they admit lack of consensus [15].

Low T_3 levels in conjunction with low or normal free T_4 and TSH levels are linked to non-thyroidal disease (euthyroid sick syndrome) [16]. In prematurity, several factors can inhibit the conversion of peripheral T_4 to T_3, including hypoxemia, acidosis, infections, hypoglycemia, hypocalcemia and malnutrition and also some rare conditions like transient secondary/tertiary hypothyroidism, transient primary

hypothyroidism and permanent primary hypothyroidism [17].

Only FT_3 was found significantly low in VLBW neonates in comparison to LBW and normal birth weight counterparts. FT_4 and TSH were also lower though statistically indifferent.

All VLBW neonates have relatively low, gestational age-dependent, thyroxine-binding globulin (TBG) concentrations associated with variably low total thyroxine (T_4) concentrations. These neonates also have a high prevalence (30%-60%) of nonthyroidal illnesses which influence thyroid function, including total and free iodothyronine concentrations. As a result, VLBW neonates manifest a high prevalence of transient primary hypothyroidism (0.41%) and transient hypothalamic- hypothyroidism (thyrotropin /TSH deficiency) (5%-10%)[18].

The TSH levels though decreased, gets normalized over a few weeks. Hence, it is known as Transient Hypothyroxinemia of Preterms (THOP) or Transient congenital hypothyroidism [19, 20]. It may be caused by iodine deficiency, maternal thyrotropin receptor blocking antibodies, maternal intake of anti-thyroid drugs, maternal or neonatal iodine exposure, loss of function mutations and hepatic haemangioma [20] or factors those that affect the pituitary-like untreated maternal hyperthyroidism, prematurity and drugs [21].

Preterm babies are remarkably susceptible to the effects of iodine deficiency, due to decreased in utero thyroidal iodine stores, immature HPT axis for T_4 production, and decreased ability to convert T_4 to T_3. Deficiency of other elements, selenium and iron may effect neurologic development and thyroidal response to iodine supplementation [22].

The maternal exposure of certain drugs like propylthiouracil or methimazole (antithyroid) or iodine antiseptics/ excessive iodine ingestion/amniofetography with iodine containing contrast may also induce transient congenital hypothyroidism [20, 23, 24] Exposure of preterms to high amounts of iodine may cause hypothyroidism due to Wolff-Chaikoff effect [25, 26].

Though the foetal HPT axis begins to function after the first trimester, its maturation is not completed till at term as evident from our data also where we found that only in term neonates FT_3 was significantly correlated to both FT_4 ($r=0.453$; $p=0.00$) and TSH ($r=0.299$; $p=0.014$). However, the exact gestational age at which this axis is developed could not be determined due to scarcity of data at individual gestational ages.

CONCLUSION

Our study concludes that maturity of HPT axis is better in term neonates than in preterm neonates. Preterm neonates also are prone to develop sick euthyroid syndrome and THOP. The incidence of THOP increases reciprocally with gestational age [27] as observed in our study also. Hypothyroxinemia without thyrotropin elevation does not require treatment, and some potential risks of levothyroxine supplementation have been reported. Although most thyroid dysfunctions are transient, careful follow-up after discontinuation of levothyroxine is considered so as to avoid missing persistent hypothyroidism [20].

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