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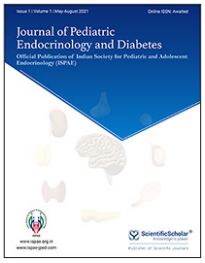

Original Article

Prevalence of congenital hypothyroidism and transient neonatal hyperthyrotropinemia in babies born to hypothyroid mothers at a tertiary care hospital

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ABSTRACT

Objectives: Transient neonatal hyperthyrotropinemia (TNH) is being increasingly recognized in the developed world as a risk factor for the development of permanent hypothyroidism. It is defined as transient elevation of serum thyroid-stimulating hormone (TSH) levels between 10 and 20 mIU/L after 48 h of life with normal free thyroxine levels, returning to normal after 2 weeks of life. Factors associated with TNH as well as its consequences on growth and development are lesser known at present. Maternal hypothyroidism, both overt and subclinical, is known to have adverse neurodevelopmental outcomes in children. Maternal hypothyroidism is also one of the risk factors for developing TNH. This study aimed to measure the prevalence of congenital hypothyroidism (CH) and TNH, and evaluate neurodevelopmental outcomes in children born to hypothyroid mothers.

Material and Methods: Sixty-three consecutive neonates born to mothers diagnosed as hypothyroid during pregnancy were enrolled for the study. Fifty neonates underwent evaluation for thyroid functions and development till 6 months of age, after excluding preterm and sick babies requiring intensive care.

Results: None of the babies had CH. The prevalence of TNH was found to be 6.0% (n = 3/50), with TSH values normalizing by 4 weeks of age. All babies with TNH were female. Development assessment done till 6 months of life was normal for all babies.

Conclusion: Our study describes the prevalence of TNH and short-term development outcomes in babies born to hypothyroid mothers. The role of TNH in the development of permanent hypothyroidism is still a debatable topic, and larger studies are needed to assess its implications on linear growth, academic performance, as well as language and intellectual development.

Keywords: Congenital hypothyroidism, Developmental quotient, Maternal hypothyroidism, Transient neonatal hyperthyrotropinemia, Thyroid-stimulating hormone

INTRODUCTION

Congenital hypothyroidism (CH) is one of the most common preventable endocrine causes of neurodevelopmental and intellectual disability in children. Transient neonatal hyperthyrotropinemia (TNH) is defined as a transient elevation of thyroid-stimulating hormone (TSH) levels (10–20 mIU/L) after 48 h of life with normal free thyroxine (fT4) levels, reverting to normal levels after 2 weeks of life.[1] Worldwide confirmed CH occurs in one out of 3500–4000 live

births, with a ratio of TNH/CH equal to 0.17/1.[2] While the true incidence of CH in India is not exactly known at present, the Indian Council for Medical Research, in a recent study conducted on 36,000 newborns, has quoted a higher incidence of 1.6 in 1000 in India.[3] TNH is being encountered more commonly in developed parts of the world where all neonates are screened routinely. Therefore, the incidence of TNH varies widely based on ethnicity, population genetics, and the variability of screening methods used.[4] Pathogenesis of TNH is multifactorial, caused by extrauterine stressors such as prematurity, low birth weight and perinatal goitrogen exposure, or intrauterine factors like maternal hypothyroidism.[5] Effects of TNH on growth and development, and the risk of persistent hyperthyrotropinemia in children with TNH are being increasingly recognized in recent studies.[6-8]

Maternal hypothyroidism, both subclinical and overt, is diagnosed in 0.3–2.5% of pregnant women[9] and is known to cause adverse pregnancy and neonatal outcomes.[10,11] Various mechanisms such as maternal iodine deficiency or excess, maternal consumption of goitrogens or antithyroid medications during pregnancy, and transplacental passage of maternal antibodies are described for altered thyroid status in babies.[12] Supplementation of hypothyroid mothers with levothyroxine has shown to substantially lower the adverse complications.[13]

There is a paucity of literature on neonatal outcomes in babies born to hypothyroid mothers, especially in the Indian scenario. This study was hence planned to measure the prevalence of CH and TNH, and evaluate the neurodevelopmental outcomes in children born to hypothyroid mothers.

SUBJECTS AND METHODS

The study was conducted at the Employees State Insurance Corporation – Post Graduate Institute of Medical Sciences and Research, New Delhi, India, as a part of a postgraduate thesis. Sixty-three consecutive neonates born to mothers diagnosed with hypothyroidism during pregnancy were enrolled over a 1-year period (January 2019–December 2019), based on convenient sampling technique in view of short study time period. All women with TSH >2.5 mIU/L in the first trimester and >3.0 mIU/L thereafter were diagnosed as hypothyroid and started on levothyroxine supplements, as per the protocol followed by the Department of Obstetrics of the institute, irrespective of anti-thyroid peroxidase (anti-TPO) antibody status (based on the Endocrine Society's 2007 Guidelines on Thyroid and Pregnancy).[14] Maternal thyroid status was followed 4–6 weekly and work-up for autoimmune hypothyroidism using anti-TPO antibody was planned for persistent hypothyroidism after pregnancy.

A written, informed consent from the parents was obtained. Birth weight, sex, APGAR score, gestation, physical examination findings, and anthropometric data were recorded. All babies were subjected to venous sampling on days 3–5 and at 2 weeks of life for thyroid function tests by chemiluminescence method. Serum TSH >20 mIU/L with fT4 <1.17 ng/dL or isolated fT4 <1.1 ng/dL were the cutoffs used to diagnose CH at 3–5 days of life,[15] while a TSH level >10–20 mIU/L at 3–5 days with normal fT4 levels, normalizing on re-examination at 2–4 weeks suggested TNH.[1] At 2 and 4 weeks of life, TSH >20 mIU/L and >10 mIU/L, respectively, with fT4 <1.17 ng/dL or isolated fT4 levels <1.17 ng/dL were the cutoffs used for diagnosing CH.[15] Children with TSH >10 mIU/L at 2 weeks were reassessed with thyroid profile at 4 weeks of life to look for delayed resolution of TNH or persistent elevation of TSH requiring treatment. Preterm, sick babies requiring intensive care, and those with APGAR score <6 were excluded from the study. Treatment as per protocol was planned for (i) children diagnosed as CH and (ii) those with persistent hyperthyrotropinemia at 4 weeks of age. Data for physical examination findings including dysmorphism, prematurity, low birth weight, and the need for intensive care were recorded on a structured proforma and used to assess neonatal outcomes.

Maternal details regarding thyroid profile at diagnosis, initiation of thyroid supplements, comorbidities, and compliance were collected.

Development assessment of all children was carried out on immunization days at 6, 10, and 14 weeks, as well as at 6 months of age using the Trivandrum Development Screening Chart (TDSC). TDSC is a simple and easy tool to assess development in children till 2 years of age. It has been validated against the Denver Developmental Screening Test and consists of 17 items to screen gross motor, social adaptive, fine motor, and language in both hospital and community settings.[16]

Descriptive statistics were applied to calculate frequencies of categorical variables, and measures of central tendencies and dispersion were used to describe continuous variables. Bivariate analysis was done for categorical variables using Chi-square test, to determine the association between various sociodemographic variables, clinical history, and risk factors with laboratory outcomes. To analyze the continuous quantitative data, Student's t-test and Mann–Whitney U test were used, based on the data distribution. P <0.05 was selected as statistically significant. Ethics clearance was obtained from the Institutional Ethics Committee.

RESULTS

Baseline characteristics

We collected data for 63 hypothyroid mothers over a period of 1 year. Majority of mothers were in the age group of 26–

30 years (47.6%, *n* = 30) followed by 18–25 years (28.6%, *n* = 18) and >30 years (23.8%, *n* = 15). Mean maternal fT4 and TSH levels at diagnosis were 0.87 ± 0.40 ng/dL and 2.82 ± 0.40 mIU/L, respectively. Most of the mothers were diagnosed as hypothyroid in the second trimester of pregnancy (60.3%, *n* = 38), followed by the first trimester (20.6%, *n* = 13) and third trimester (19%, *n* = 12), and all received levothyroxine at recommended doses. There was 100% compliance and no loss to follow-up. Anemia (41.3%), bronchial asthma (11.1%), pre-eclampsia (11.1%), hypertension (9.5%), and gestational diabetes (7.9%) were the most common comorbidities. Majority of the mothers had term delivery (81%, *n* = 51) and the mean birth weight of babies was 2.72 ± 0.49 kg (range 1.7–4.0). Twenty-three babies (36.5%) had low birth weight (<2.5 kg). Vaginal birth was the most common mode of delivery (55.6%, *n* = 35) followed by lower segment cesarean section (LSCS) (34.9%, *n* = 22). No significant difference was obtained on comparing maternal TSH levels among neonates with low and normal birth weight (*P* = 0.32).

Males comprised 60% (*n* = 38/63) and females comprised 40% (*n* = 25/63) of the neonates [Table 1]. There was no dysmorphism or malformation in any of the neonates. All had APGAR scores of >6 at 1 and 5 min of birth (range 7–9). Five neonates (8.0%, preterm = 4, term = 1) required intensive care and mean duration of stay in intensive care unit was 6.75 ± 2.87 days (range 3–10). Sepsis (*n* = 2/5) and respiratory distress (*n* = 2/5) were the most common indications for intensive care unit admission followed by seizures (*n* = 1/5).

Table 1: Baseline characteristics of babies and thyroid profile of hypothyroid mothers (*n*=63).

Variables	Observations (*n*=63)
Gestation (>37 weeks)	51/63 (80.9%)
Sex (female)	25/63 (39.6%)
Birth weight (mean±SD*) (kg)	2.72±0.5
Babies requiring intensive care	5/63 (8.0%)
Maternal fT4 level (mean±SD) (ng/dL)	0.87±0.4
Maternal TSH level (mean±SD) (mIU/L)	2.82±0.4
Mothers with subclinical hypothyroidism (isolated increase in TSH)	42/63 (66.7%)
Mothers with overt hypothyroidism (increased TSH and fT4 <0.7 ng/dL)	21/63 (33.3%)
Mothers with clinical hypothyroidism/ goiter	Nil

*SD: Standard deviation

Table 2: Thyroid functions at 3–5 days, 2 weeks, and 4 weeks of life.

Thyroid functions	Results in cases (*n*=50)		
	3–5 days (*n*=50)	2 weeks (*n*=50)	4 weeks (*n*=2)
TSH (mIU/L) mean±SD	3.82±2.69	3.66±2.43	3.25±1.90
fT4 (ng/dL) mean±SD	2.43±1.43	2.52±1.32	2.34±1.21
TSH >10–20 mIU/L	3/50 (6.0%)	2/50 (4.0%)	Nil
TSH <10 mIU/L	47/50 (94.0%)	48/50 (96.0%)	2/2 (100%)

Thyroid functions and developmental outcome

Table 2 depicts the mean TSH and fT4 levels at 3–5 days, 2 weeks, and 4 weeks of life. Out of 63 neonates, 13 neonates (preterm and those requiring intensive care) were excluded from the study. Thyroid and development screening were performed over 50 neonates. Three out of 50 (6.0%) neonates had TSH levels between 10 and 20 mIU/L with normal fT4 levels at 3–5 days of life, while the rest had normal TSH and fT4 levels. At 2 weeks of life, two out of the above three neonates had TSH levels between 10 and 20 mIU/L. At 4 weeks, all neonates had normal TSH/fT4 levels. On comparing neonates with TSH levels >10 mIU/L and <10 mIU/L, no significant difference was obtained in maternal TSH levels, birth weight, growth parameters at 3–5 days of life, and development assessment at each visit. Development assessment of all babies by TDSC was normal till 6 months of life [Table 3].

DISCUSSION

In this hospital-based cross-sectional study, two important short-term outcomes are highlighted, namely, the prevalence of TNH and the development status in children born to hypothyroid mothers. None of the 50 neonates screened had CH, but the prevalence of TNH was found to be 6.0%. Out of the three neonates with TSH >10–20 mIU/L, two neonates had elevation of TSH >10 mIU/L at 2 weeks which normalized by 4 weeks of life. In contrast to available literature on TNH, we observed a delay in resolution of hyperthyrotropinemia by 4 weeks of age, however, no adverse effects on growth and development were noted.

In a study done by Anjum *et al.* to determine the frequency of CH in neonates, four out of 550 neonates had elevated TSH levels (0.8%) and significant association was noted between CH and maternal hypothyroidism.[17] Similar observations were made by Manglik *et al.* who confirmed CH in two out of 1200 neonates (0.16%), having significant association with maternal hypothyroidism.[18] In contrast, in a study conducted by Shravani *et al.* to evaluate thyroid functions in neonates born to hypothyroid mothers, none of the neonates had hypothyroidism or clinically significant low birth weight. Mothers were screened early in pregnancy before 18 weeks of gestation and received timely treatment.[19] In our study, majority of mothers were screened in the second trimester.

Table 3: Comparison of baseline variables and outcomes in children with TSH <10 and TSH >10 mU/L at 3–5 days of life.

Variables	TSH <10 mU/L (*n*=47)	TSH >10 mU/L (*n*=3)	*P*-value
Birth weight (mean±SD) (kg)	2.82±0.42	2.88±0.46	0.81
Length at 3–5 days (mean±SD) (cm)	49.25±1.72	49.12±2.24	0.90
HC* at 3–5 days (mean±SD) (cm)	33.91±1.26	34.52±1.47	0.42
Sex (females)	18/47 (38.2%)	3/3(100%)	0.03
Mean maternal TSH level (mean±SD) (mIU/L)	2.86±1.85	3.58±0.34	0.50
DQ# at 6 months of age (mean±SD)	98.9±3.73	97.2±4.80	0.45

*HC: Head circumference. #DQ: Developmental quotient: (Developmental age/chronological age)*100

Although none of the neonates developed CH, TNH was observed as described above.

In a large longitudinal study by Cuestas *et al*., 301 out of 5040 normal term newborns had TNH (6.0%).[1] A significant proportion of babies with TNH were female (*n* = 193, 64%), and on follow-up after 6 years, six of out of 65 randomly selected TNH cohort had permanent hypothyroidism (9.2%). There was no effect on linear growth, however, lower development scores were observed in the TNH cohort as compared to controls. Low birth weight babies, preterm birth, and babies born to mothers with immune thyroid disease were excluded in their study. In a study conducted by Garg *et al.* in India, the prevalence of TNH was found to be 1:47, and two neonates with TNH were found to have low development quotient score as well as deranged thyroid profile at 3 months of age.[20] Maternal autoimmunity, maternal thyroid dysfunction, and female sex were significantly associated with TNH, and low urinary iodine levels were significantly associated with maternal autoimmunity.

In the present study, all babies with TNH were female (*n* = 3/50), suggesting a possible role of maternal autoimmunity as a risk factor for hyperthyrotropinemia in infants. Since author's institute provides health benefits to economically weaker section of society (primarily workers of factories, including migrants), the iodine status in pregnancy and lactation may be poor as compared to higher socioeconomic section of the community, which could be another factor contributing to TNH. A study by Roy *et al.* conducted on rural population of West Delhi, found iodine deficiency in pregnant women of lower socioeconomic status,[21] despite an improvement in percentage of households using iodized salt being more than the national average in Delhi (98.5%), as observed under the National Health and Family Survey 2015–2016.[22] In contrast to Cuestas *et al.* and Garg *et al*., development status of all infants was normal till 6 months of age in the present study.

Maraka *et al*., in a systemic review, described higher risk of preterm delivery, placental abruption, pregnancy loss, and neonatal death in pregnant hypothyroid mothers as compared to euthyroid mothers.[23] Untreated hypothyroidism in pregnancy has also been associated with increased risk of hypertension in mothers and increased risk of low birth weight in their babies.[24] In our study, we did not identify any significant association of adverse maternal or neonatal outcomes with maternal hypothyroidism. Twelve out of 63 mothers had preterm delivery (19%), which was comparable to our hospital's census. Twenty-three babies (36.5%) had low birth weight and no statistically significant association was found between low birth weight and maternal TSH values. One out of three babies with TNH had low birth weight. This could possibly be explained by adequate maternal control of hypothyroidism with levothyroxine supplementation, compliance to therapy, absence of overt clinical hypothyroidism among mothers, and small sample size.

CONCLUSION

This study is one of the few Indian studies conducted to find out the prevalence of CH and TNH in children born to hypothyroid mothers. Role of TNH in the development of permanent hypothyroidism as well as its effects on growth and development is still a debatable topic, and larger and long-term studies are needed to assess its implications on linear growth, academic performance, language, and intellectual development. We emphasize on early screening of mothers for hypothyroidism in pregnancy and screening of all newborns for CH as they benefit most from early initiation of treatment. In addition, larger studies are needed to compare the prevalence of TNH in babies born to euthyroid and hypothyroid mothers.

Limitations and future scope

Small sample size due to short study time period is a major lacuna in diagnosing CH. Due to financial constraints specific autoimmune work-up including anti-TPO antibodies, TSH receptor antibodies, iodine profile, and thyroid profile of all neonates born during the study period could not be done. In addition, we did not have a control group for development assessment. Babies enrolled in the study are still under regular follow-up for development status and the authors plan to report a long-term follow-up in future.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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