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ORIGINAL RESEARCH

Congenital hypothyroidism and developmental outcome in preterm and term babies born to hypothyroid mothers

Dr. Dushyant Rastogi[1], Dr. Manoj Kumar Singh[2], Dr. Anita[3]

[1]Assistant Professor, [2]Professor, Department of Pediatrics, K.M. Medical College and Hospital, Pali Dungra, Sonkh Road, Mathura, Uttar Pradesh, India
[3]Assistant Professor, Department of General Medicine, K.M. Medical College and Hospital, Pali Dungra, Sonkh Road, Mathura, Uttar Pradesh, India

Corresponding author
Dr. Dushyant Rastogi
Assistant Professor, Department of Pediatrics, K.M. Medical College and Hospital, Pali Dungra, Sonkh Road, Mathura, Uttar Pradesh, India
Email: dushyantrastogi2011@gmail.com

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ABSTRACT

Background: The clinical manifestations of congenital hypothyroidism (CH) are often subtle and not evident at birthand so many newborn infants remain undiagnosed in the absence of routine newborn screening. This delay in the diagnosis leads to the most severe outcome of CH which is mental retardation. CH isone of the most common preventable causes of mental retardation. **Aim:** To determine the prevalence of CH in preterm and term neonatesborn to hypothyroid mothers, assessment of their physical parameters at birth; growth and neurodevelopment till 6 months of age. **Methods:** The study was conducted at K.M. Medical College & Hospital, Mathura as a prospective observational study from April 2022 to September 2023after obtaining clearance from institutional ethical committee. Fiftyconsecutive pregnant hypothyroid mothers suffering from subclinical and overt hypothyroidism were enrolled over a period of 12 months. They were started on levothyroxine andgood compliance was ensured. **Results:** Out of 50 babies born, 45babies were included in the study while 5 were excluded as they required admission in neonatal intensive care unit. None suffered from CH requiring treatment. Only 4 babies have TSH > 20 mIU/L (<40 mIU/L) with normal fT4 at 72 hours of life but, later it normalized at 2 weeks of life. There was nostatistically significant differencein the anthropometric measurements between preterm and term babies. All babies were followed up to 6 months of age and assessedfor their neurodevelopment which was found to be normal. **Conclusions:** Early diagnosis of hypothyroidism in pregnancy and its timely treatment prevents CH in neonates and promotes their adequate growth and neurodevelopment. Also, there should be screening of newborns for CH as they will have maximum benefit from early initiation of treatment.

Keywords: Congenital hypothyroidism, Developmental quotient, Maternal hypothyroidism

INTRODUCTION

Congenital hypothyroidism (CH) is not only one of the most common congenital endocrine disorders in infants but also a common preventable cause of intellectual disability. Thyroid hormone plays a crucial role in the development of brain during the first 2-3 years of life and hence early diagnosis and intervention are of utmost importance in cases of CH. After diagnosing the disorder early, neuro-developmental outcome is generally normal if the treatment is started within a few weeks of birth.[1] The clinical features of congenital hypothyroidism are often subtle and thereby making the early diagnosis of CH at birth very difficult. These features later become evident if diagnosis is missed or treatment is delayed or suboptimal.[2]

Maternal hypothyroidism, both subclinical and overt, is diagnosed in 0.3–2.5% of pregnant women and is known to cause adverse pregnancy and neonatal outcomes.[3] 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.[4] Supplementation of hypothyroid mothers with levothyroxine has shown to substantially lower the adverse complications.[5]

There is a paucity of literature on neonatal outcomes in babies born to hypothyroid mothers, especially in

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the Indian scenario. This study was hence planned to measure the prevalence of CH andto evaluate any significant difference in thyroid status and neurodevelopmental outcome of preterm and term neonates born to hypothyroid mothers.

OBJECTIVES

- To study the prevalence of CH in babies born to hypothyroid mothers.
- To study neonatal outcomes in terms of gestation, birth weight, length, head circumference and admission in neonatal intensive care unit (NICU).
- To study the growth and neurodevelopment of these infants till 6 months of age.

MATERIAL AND METHODS:

A prospective observational study was conducted at the Department of Pediatrics in KMMCH, Mathura for 18 months (April 2022 to September 2023) in active collaboration with OB- GYN department. Written informed consentwas taken from the mothers before including into the study. A total of 50 consecutive pregnant mothers suffering from subclinical or overt hypothyroidism coming to our hospital during one year starting from April 2022, were enrolled in the study. All mothers registered were in either 1st or 2nd trimester of pregnancy. Institutional ethical committeeclearance was taken. A written and informed consent was obtained from the mothers.A detailed medical as well as maternal history was taken and treatment details were obtained. If any of the pregnant motherwas suffering from any medical illness or any pregnancy related problems like gestational diabetes, hypertension, preeclampsia, bad obstetric history etc. were excluded from the study.

The general physical examination and obstetric examination wasdone and recorded by doctors ofdepartment of Obstetrics & Gynecology in the antenatal clinic. Routine investigations including the thyroid function were assessed. They were all screened for TORCH infection. Ultrasound examinations were done at 18-20 weeks for gestational age, and to rule out major structural anomalies.Venous sample was taken for TSH and fT4 estimation and serum was processed within 24 hours of collection of samples.

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 irrespective of the presence of antibodies to thyroid peroxidase (TPO) or thyroglobulin (TG) status according to the Endocrine Society's 2007 Guidelines on Thyroid and Pregnancy.[6] Maternal thyroid status was followed 4–6 weekly and work-up for autoimmune hypothyroidism using anti-TPO and anti-TG antibodies could not be done due to financial constraints. They were started on levothyroxine supplements and followed up as per protocols. The compliancefor levothyroxinein mothers was checked on follow up visits at our hospital and supplemented by local health visitors in outreach areas and was found to be good.

Inclusion criteria

- Newborns born to mothers with hypothyroidism

Exclusion criteria

- Mothers having high risk pregnancy
- Congenital anomalies
- APGAR score <6
- Sick neonates requiring admission in NICU

Venous sampling was performed after 48 hours of life on day 3 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 according to ISPAE guidelines 2018. If serum TSH >20 mIU/L with fT4 <1.17 ng/dL or isolated fT4 <1.1 ng/dL at 3-5 days then thyroid profile was repeated at 2 weeks. [7] Children with TSH >10 mIU/L at 2 weeks were reassessed with thyroid profile at 4 weeks of life to look for persistent elevation of TSH requiring treatment.

Development assessment of all children was done on routine vaccination visits at 6, 10, and 14 weeks, as well as at 6 months of age using the Trivandrum Development Screening Chart (TDSC). TDSC was designed and developed at Child Development Centre, SAT hospital, Trivandrum and consists of 17 items to assess development in children till 2 years of age.It has been validated against the Denver Developmental Screening Test in both hospital and community settings.[8]Forthe analysis of continuous quantitative data, Student's t-test was used. P <0.05 was selected as statistically significant.

RESULTS

At our centre, we collected the data of 50 hypothyroid mothers over a period of 12 months. 5 were excluded as their babies required intensive care. Out of these 45 mothers, 29 mothers (64.4%) were having subclinical hypothyroidism (isolated increase in TSH) while 16 (35.5%) suffered from overt hypothyroidism (raised TSH with fT4<0.7 ng/ml). All mothers received levothyroxine with good compliance. Mean maternal TSH and fT4 levels of preterm and term babies was not found to be statistically significant.

Most of the babies were born by vaginal route (88%, n=44) and rest by cesarean section (12%, n=06). Out of total 50 neonates, 10 (20%) babies were preterm and 40 (90%) were term. 5 (20%) babies were having APGAR score≤6 while 2 (10%) babies required bag and mask ventilation at the time of birth. 3 preterm and 2 term babies required admission in NICU and were excluded from the study. The 3 preterm babies suffered from respiratory distress while one term baby had meconium aspiration syndrome and the other suffered from transient tachypnea of newborn.

Out of total 45 neonates included in study, 7 babies (15.5%) were preterm and 38 (84.4%) were term. The

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preterm and term babies born were not having any statistically significant difference in their birth weight, length, and head circumference. None suffered from CH or any congenital malformations. Only 4 out of 45 (8%) babies has TSH > 20 mIU/L (TSH = 20-40) with normal fT4 at 72 hours of life. Out of 4, 3 were preterm and 1 was term baby. Thyroid profile repeated at 2 weeks and 4 weeks was found to be normal (TSH <10 mIU/L; normal fT4). This may also suggest transient congenital hypothyroidism (TCH) which may have developed as a result fetal exposure to maternal antithyroid antibodies which we were not able to assess due to unavailability at our institution and poor affordability of patients. Development assessment by TDST till 6 months was normal in all babies.

Table I: Relation of gestational age of babies with Thyroid profile of hypothyroid mothers

Variables	Preterm babies(n=7)	Term babies(n=38)	P-value
Mean Maternal TSH (mean±SD) (mIU/L)	2.114± 1.228	3.076± 2.226	0.275
Mean Maternal fT4 (mean±SD) (ng/dl)	0.986± 0.393	0.876± 0.407	0.998

Table II: Outcome of babies born to hypothyroid mothers

Deliveries by Vaginal route (n=44)	Deliveries by C-section (n=6)
Male babies (n=22)	Female babies (n=28)
Preterm babies (<37 weeks) (n=10)	Term babies (>37 weeks) (n=40)
Babies with weight >2500 grams (n=28)	Babies with weight <2500 grams (n=22)
Healthy babies (n=45)	Sick babies (n=05)
APGAR score>6 (n=45)	APGAR score≤6 (n=05)
Babies requiring resuscitation at birth (n=2)	Babies not requiring resuscitation at birth (n=48)

Table III: Comparison of baseline variables, Thyroid profile, and Developmental Outcomes in Preterm and Term neonates

Variables	Preterm babies(n=7)	Term babies(n=38)	P-value
Birth weight (mean±SD) (kg)	2.40± 0.447	2.77± 0.485	0.067
Length (mean±SD) (cm)	47.88± 1.560	48.51± 1.830	0.398
Head circumference (mean±SD) (cm)	32.31± 0.958	33.11± 1.249	0.114
TSH (at 3-5days) (mean±SD) (mIU/L)	5.15± 7.081	5.86± 5.793	0.774
fT4 (at 3-5days) (mean±SD) (ng/dl)	1.91± 0.866	2.47± 1.798	0.429
Developmental Quotient at 6 months of age (mean±SD)	96.24± 2.480	97.81± 3.290	0.237

DISCUSSION

Congenital hypothyroidism (CH) affects approximately in 1:4000-1:1100 newborn, out of which eighty five percent are sporadic cases of thyroid dysgenesis. Next in the frequency are genetic disorders with reported mutationsof genes for PAX-8, thyroid transcription factor 2,TPO, Thyroglobulin, Sodium iodine symporter and others. Neonatal screening programmesare now implemented throughout the world and have reduced the need for special evaluationto only 10% of CH children. Hence the need for early detection and prompt treatment withLevo-thyroxine is required for adequate neurodevelopment of the babies.

The present study was a descriptive, cross-sectional, hospital-based study conducted onbabies of hypothyroid mothers presenting in the department of Pediatrics, KMMCH, Mathura for 18 months. The study was aimed to find out the prevalence ofhypothyroidism in the babies born to hypothyroid mothers along with factors associated withit. Total 50 pregnant women who were diagnosed as hypothyroid during pregnancy and theirbabies were enrolled and followed upto 6 months of age.

In our study, mother's age ranged from 18 years to 39 years. Mean age of the mothers was26.5 ±5.6 years. Similar results were reported in a study conducted by Anjum et al in whichmothers age ranged from 18-40 years with the mean age of 26±4 years.[9] In another study byAdeniran et al, most of the mothers were above 25 years.[10]

Maximum mothers (47.6%) were in 26-30 years of age group in our study which is similar to a study by Seeralar etalin which 46% mothers were in this age group.[11]Out of 50 mothers, 42(84%) were booked while 8(16%) were unbooked and most of the mothers were diagnosed in second trimester38(76%) followed by first trimester i.e.12(24%).

In current study, most of the mothers 40(75%) had term delivery while 10(25%) mothershad preterm delivery which is comparable with our hospital's census. This was supported bystudy by Adeniran et alwhere authors found majority of newborns between 37 weeks and39 weeks of gestational age.[10] Another study by Nirmala et al found the frequency ofpreterm labour as 25.6% in hypothyroid mothers.[12] The results of our study contrast withresults of study by Anjum et al in which 99% babies were born at gestational age of 37-40weeks and 1% babies were

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born at gestational age >40 weeks.[9] Similarly, in another study bySeeralar et al which included 1695 babies, 6.3% were born at less than 37 weeks and 93%at more than 37 weeks.[11] This variation may be due to difference in inclusion and exclusioncriteria of the studies as authors did not include preterm babies in their studies.

In current study, 44(88%) mothers had normal vaginal delivery and 6(12%)by LSCS, which contrasts with study by Seeralar et alwhich reported 65% of deliveries bycaesarean mode and 35% were normal vaginal deliveries.[11]

The present study revealed that, among the 50 babies, 22(44%) were males and 28(56%) werefemales. There was female preponderance, with the male to female ratio of 0.78:1 which contrasts with results reported by Anjum et al which was 1.1:1.[9] Study by Sanjeev et al reported even higher male to female ratio of 1.52:1.[13] Other international and national studies also reported almostequal proportion of male and female babies.[14-16] Higher preponderance of female babies in ourstudy can be due to relatively small sample size.

In our study, out of total 50 babies, 22 (44%) had birth weight <2.5 kg and 28 (56%) hadbirth weight above 2.5 kgs while Seeralar et al observed only 16.5% low birth weight babies in their study.[11]Saki et al intheir study had showed statistically significant association between maternalhypothyroidism and IUGR. They found 13.7% babies with IUGR in their study and also observed that clinical hypothyroidism was associated with increased risk of preterm delivery.[17]

Few other studies have also corroborated this finding that maternal hypothyroidism isassociated with low birth weight of baby.[18,19] None of the babies had weight more than 4000 grams.

In our study we observed low APGAR score in 10% babies which is like the study done by Saki et al 13.7%.[17]

All newborn experience a state of TSH elevation after birth due to different stimuli, eitherexposure to cold in ambient atmosphere or perinatal stress that may reach some very highlevels during the first 36 hours of life which reverts to normal soon.

In our study, we found that none of the total 45 neonates included in the study born to hypothyroid mother had CH,but prevalence of transient elevation of TSH in newborns who were born to hypothyroidmothers was 8% on day 3-5 of life after birth. Out of 45 newborns, 41 (91.1%) had TSHlevel below 10 µIU/mL on day 3-5 of their life. Only 4 newborns had TSH level above 20µIU/mL on day 3-5 (with normal fT4) which normalized to below 10 µIU/mL at 2 and 4 weeks of life. Similar to our study, Anjum et al revealed that 4 (0.8%)newborns born to hypothyroid mothers had elevated TSH level.[9]Manglik et al in their studyfound 22 (1.83%) babies out of 1200 had TSH >20 µIU/mL within first 24 hour of life andrepeat testing on day 7 of life confirmed CH in 2 babies, showing prevalence of CH 0.16%.[20]

Van Tijn et al conducted their study on a larger scale (385,000 newborns over 2 yearsperiod) and found 19 cases of CH with permanent brain damage.[21]Seeralar et al hadreported prevalence of hypothyroidism among infants as 1.7 per 1000.[11]In our study no newborn suffered from CH although 4 had TCH. Thus, this differencemay be due to large sample size in above mentioned study as compared to our study. Inanother study by Shravani et alin which sample size was relatively small, none of the 106neonates born to hypothyroid mothers had abnormal TSH and T4 and results of this study arein coherence with our study.[22] Another reason for normal TSH and T4 levels in these neonatescould be that all mothers were on regular thyroxine therapy, had good compliance and goodfollow-up.

In our study, we did not find any statistically significant association between mean maternal TSH and fT4 levels of preterm and term babies born to those mothers.

In our study, all the newborns had normal length and head circumference at the time of birthand normal growth and development was observed till 6 months of age. There was nostatistically significant difference observed in anthropometric measurements at the age of 3-5days between preterm and term babies.

All newborns enrolled in our study were followed up to 6 months of their age and assessedfor their neurodevelopment. All were found to be neurodevelopmentally normal whenassessed at 6, 10, 14 weeks and 6 months of age by TDST. This can be attributed to no baby beinghypothyroid and exclusion of newborn requiring intensive care. This issimilar to results of study by Shravani et al in which no newborn was found to behypothyroid and had normal neurodevelopment.[22]

Serial monitoring of free T4 levels along with TSH was done at day 3-5, then at 2 weeks andat 4 weeks (if required). In our study, we had four babies (out of 45) with TSH value morethan 20 µIU/mL with normal fT4 values at 72 hours of life,which normalized at 2 weeks of age (TSH <10 µIU/mL). Optimal levelsof thyroid hormone in mother prevented development of thyroid deficient state in newborns.

Compared to those children born to euthyroid mothers, children born to mothers with hypothyroxinemiawere significantly more likely to show signs of intellectual impairment. In astudy by Haddow et al, it was found that children of hypothyroid mothers had their averageIQ scores lower than matched controls and this difference is markedly increased if mother isuntreated during pregnancy.[23]However, inour study, we found no association between maternal hypothyroidism and cognitivedevelopment of child till 6 months of age. It is similar to results of study by Oken et al, whichfound that maternal TSH levels were not associated with child cognitive test scores at age 6months to 3 years.[24]Another reason for normal neurodevelopment in infants in our studycould be due

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to the fact that all mothers were on thyroxine therapy after they were foundhypothyroid. All mothers on thyroxine therapy were clinically euthyroid.

The early detection and appropriate treatment of CH is associated with normal neurodevelopment. This study shows that none of the baby born to adequately treated hypothyroid mothers suffered from CH but may suffer from TCH. 90% (n=45) of the babies were healthy at the time of birth. This states the importance of early diagnosis and timely treatment of mothers suffering from hypothyroidism in pregnancy. All newborns should be screened for CH as they will have maximum benefit from early initiation of treatment.

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