RESEARCH PAPER

Maternal Overt Hypothyroidism and Neurobehavioral Outcome of Neonates: A Cohort Study from an Iodine-deficient Area of Northern India

***Mohammad Ashraf Ganaie, Bashir A Charoo, Riyaz Ahmad Sofi, Asif Ahmed and Javeed Iqbal Bhat**

*From Department of *Endocrinology, AIIMS, New Delhi; and Department of Pediatrics, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, J&K; India.*

Correspondence to: Dr Javeed Iqbal Bhat, Department of Pediatrics, SKIMS Soura, Jammu and Kashmir 190 011, India. drjaveediqbal@gmail.com.

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Objective: To study the relation between maternal overt hypothyroidism and neurodevelopmental outcome of neonates in iodine-deficient region of Northern India (Kashmir Valley).

Design: Prospective cohort study.

Setting: Endocrinology department of a tertiary-care hospital.

Participants: 82 hypothyroid pregnant women were enrolled and followed up till delivery. The neonates born to this group represented the case neonates. 51 euthyroid healthy pregnant women were selected as control group. The neonates born to these mothers served as controls.

Main outcome measures: Early neonatal behavioral assessment at 3-4 weeks of age.

Results: The mean TSH and free T4 in neonates of mothers with well controlled hypothyroidism was significantly different from those born to mothers with poorly controlled hypothyroidism and controls in 1st trimester, but the difference was statistically insignificant for 2nd and 3rd trimester values.

Conclusion: Overt maternal hypothyroidism in iodine-deficient area constitutes a risk factor for an abnormal neurobehavioral development of affected child.

Keywords: *Infant, Iodine deficiency, Neurodevelopment, Pregnancy, Prognosis.*

Hypothyroidism is a relatively common condition among pregnant women [1,2]. During pregnancy, thyroid gland is subjected to stress and undergoes adaptation to maintain sufficient output of thyroid hormones for both the mother and the fetus [3]. In iodine-deficient areas like sub-Himalayan belt, predominant cause of hypothyroidism among pregnant women is iodine deficiency [5]. Studies have established the link between maternal hypothyroidism and adverse neurobehavioral outcome of the affected child [6]. Most of such studies were conducted in iodine sufficient areas where autoimmune thyroiditis is a predominant cause of hypothyroidism. We aimed to study the relation between maternal overt hypothyroidism and neurodevelopmental outcome of neonates in an iodine deficient region [7] of Northern India (Kashmir valley).

Methods

This prospective study was conducted over a period of 2 years at Sher-i-kashmir Institute of Medical Sciences Srinagar, a tertiary-care hospital in Northern India. The study cohort was selected from the Endocrinology department of the Institute. Eighty-two hypothyroid pregnant women receiving thyroxine/no treatment were enrolled and followed up till delivery. The neonates born to this group represented the case neonates. Fifty-one euthyroid healthy pregnant women, free from any systemic disease, were selected as controls from the same institute. The neonates born to these mothers served as control neonates.

Ethical clearance was obtained from institutional ethical committee (IEC) and written informed consent was taken from all participants. All pregnant women were closely followed till delivery and their neonates were followed up till 1 month of age.

The study participants were categorized into following subgroups: *Group A* (n=43) – known hypothyroid women on treatment but uncontrolled at presentation and women first time diagnosed with hypothyroidism during first trimester of pregnancy; *Group B* (n=39) – known hypothyroid women on treatment having good control; and *Controls* (n=51) – euthyroid women without any treatment. *Neonates*: 132 neonates born to case (81) and control (51) group mothers were included in this study. There was one still birth in the case group.

In each trimester, estimation of serum TSH and free thyroxine (FT4) levels were done by chemiluminescence

method. Simultaneously, 3 mL of urine was also collected in each trimester and immediately stored at –70^{0}C for urinary iodine estimation. Urinary iodine estimation was done by Sandell-Kolthoff reaction principle and all the stored samples were processed together at the end of study period. All the enrolled neonates underwent thyroid screening anytime from 2nd day to 6th day of life by above mentioned method. Levels less than 10 mU/L were considered to be normal, 10-20 mU/L were considered borderline and >20 mU/L were labelled as abnormal. Borderline group was recalled for estimation of thyroid status after 2-4 weeks.

Early neonatal behavioral assessment was done at 3-4 weeks of age using Brazelton's Neonatal Behavioral Assessment Scale (NBAS). The scale contains 7 clusters of 31 items, both neurological and supplementary, that measures the quality of responsiveness and the amount of input that the infant needs from the examiner to show his or her best performance. All of the items were scored in the correct state as defined in the NBAS guidelines. ANOVA (analysis of variance) was used for parametric data and Kruskal Wallis test was used for non-parametric data after checking for Gaussian distribution with the help of Shaprio-Wilk and Kolomogrov-Smirnov tests. Graph-pad prism statistical software was used for analyses.

RESULTS

This hospital-based study comprised of 82 mothers with hypothyroidism and 51 control mothers. The mean (SD) age of cases and controls was 29.4 (3.5) and 29.9 (3.4) years, respectively. ***Table* I** compares anthropometric parameters in case and control neonates. ***Table* II** presents thyroid function tests in the mothers in 1st, 2nd and 3rd trimester. The mean TSH in group A was higher in 1st trimester than Group B and controls but the difference was statistically insignificant in 2nd and 3rd trimester. First trimester FT4 levels were lower in group A compared to group B pregnant women and controls. In all three groups, mean urinary iodine excretion in all trimesters was less than 150 µg/dL. Total T4 was significantly higher in group A and Group B Neonates than control neonates. The mean (SD) NABS score in group A [19.6 (2.15)] was significantly lower than group B [21.3 (3.72)] (*P*.0.037) and group C [24.0 (3.20)] (*P* <0.001). Moreover, the NABS scrore in group B was also significantly lower than controls (*P*<0.001).

TABLE I ANTHROPOMETRIC PARAMETERS IN THE THREE GROUPS

	Group A (n=43)	*Group B (n=39)*	*Control (n=51)*	*P value*
Weight (kg), mean (SD)	2.42 (0.31)	2.67 (0.38)	2.79 (0.41)	<0.001
Length (cm), mean (SD)	47.8 (1.66)	48.4 (1.46)	48.2 (1.61)	0.25
Head circumference (cm), mean (SD)	33.7 (1.51)	34.2 (1.26)	34.3 (1.11)	0.07
Gestational age (wks), mean (SD)	36.0 (1.75)	36.7 (0.98)	36.7 (0.70)	0.02

Group A= Born to mothers with uncontrolled hypothyroidism at presentation;. Group B = Born to mothers with good control at presentation; Control=Born to euthyroid mothers.

TABLE II COMPARISON OF THYROID FUNCTION PARAMETERS [MEADIAN (IQR)] IN THE THREE GROUPS

Variable	*Group A, n=43*	*Group B, n=39*	*Control, n=51*	*P value*
1st trimester TSH (µIU/mL)	7.13 (3.93)	3.60 (2.78)	4.50 (1.12)	<0.001
1st trimester FT4 (ng/dL)	1.09 (0.31)	1.26 (0.43)	1.47 (0.32)	<0.001
1st trimester urinary iodide (mcg/L)	139.2 (23.05)	144.7 (19.5)	144.2 (17.31)	0.078
2nd trimester TSH (µIU/mL)	5.04 (4.22)	3.98 (2.66)	4.87 (0.65)	0.070
2nd trimester FT4 (ng/dL)	1.08 (0.30)	1.07 (0.32)	1.11 (0.20)	0.276
2nd Trimester Urinary Iodide (mcg/L)	127.1 (20.8)	131.7 (21.0)	133.09 (16.70)	0.054
3rd Trimester TSH (µIU/mL)	5.55 (3.91)	4.62 (3.1)	5.25 (0.46)	0.127
3rd Trimester FT4 (ng/dL)	1.06 (0.23)	1.06 (0.2)	1.11 (0.23)	0.092
3rd Trimester Urinary Iodide (mcg/L)	117.0 (24.97)	120.0 (21.2)	121.40 (16.79)	0.027

Group A= uncontrolled hypothyroidism. Group B = controlled hypothyroid; Control = Euthyroid pregnant women.

WHAT IS ALREADY KNOWN?

- Hypothyroxinemia of pregnancy is a risk factor for adverse neurodevelopmental outcome in offspring.

WHAT THIS STUDY ADDS?

- Maternal overt hypothyroidism in this iodine-deficient area was associated with adverse neurodevelopmental outcomes in the offspring.

DISCUSSION

Our study demonstrates that iodine deficiency is still prevalent in our population and iodine intake in our pregnant women is inadequate as median urinary iodine level was less than recommended median value of 150 μg/L [8] in all the 3 groups of patients. We also demonstrated that neurobehavior development of neonates born to hypothyroid mothers is lower in comparison to euthyroid mothers.

These results are in agreement with an earlier study [6] in which maternal hypothyroxinemia (low FT4, normal TSH) in the first trimester was associated with decreased NBAS (orientation) scores. However, this study was conducted in an iodine-sufficient area and included women with hypothyroxinemia of pregnancy with no overt hypothyroidism. Mothers in our study were overt hypothyroid with markedly elevated TSH and decreased FT4 in first trimester, and most of them were on thyroxine replacement.

The limitation of our study was that neurobehavioral assessment in our cohort was done between 3-4 weeks of postnatal age that may not be representative of future neurodevelopment of a child. Studies where assessment was done at a later age also support this observation [9,10]. Long term follow-up studies evaluating the causal link between maternal hypothyroidism and adverse neurodevelopmental outcome in the affected offsprings are required.

To conclude, our study suggests an important link between early maternal hypothyroidism and neurobehavioral outcome of affected offsprings. We recommend early identification of hypothyroidism in pregnant women, especially in endemic areas. and their optimal treatment to improve developmental outcome of their children.

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