RESEARCH PAPER

Association Between Neonatal Thyroid Stimulating Hormone Status and Maternal Urinary Iodine Status

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Background: Maternal urinary iodine concentration (MUIC) and percentage of neonates with Thyroid stimulating hormone (TSH) >5 mIU/L are amongst the parameters suggested for assessing adequate iodine status.

Objective: To assess the correlation between MUIC and neonatal TSH levels.

Study design: Cross-sectional.

Settings: Tertiary care center in Delhi, India, between November 2015 to November 2016.

Participants: Postnatal mother-neonate dyads.

Methods: TSH levels assessed among neonatal samples were stratified as below and above 5 mIU/L. MUIC was measured in 544 mothers, 400 mother-neonate dyads with neonatal TSH levels >5 mIU/L (cases) and 144 mother-neonate newborn mother dyads with neonatal TSH <5 mIU/L (controls).

Results: The percentage of mothers with iodine insufficiency (9.8% *vs* 5.6%) as well as iodine excess (54.3% *vs* 41.7%) were significant higher in cases than controls. Mean TSH was also higher (*P*=0.0002) in both the iodine deficient and iodine excess group. There was no correlation between neonatal TSH values and MUIC.

Conclusions: Lack of correlation between neonatal TSH and MUIC is due to iodine excess together with iodine deficiency.

Keywords: *Newborn screening, Postpartum, Povidone iodine, Pregnant, TSH*.

Iodine is crucial for the production of thyroid hormones and hence an important determinant of maternal and neonatal health. Pregnant women and newborn children are most vulnerable to Iodine deficiency disorders (IDD) [1]. As per World Health Organization (WHO), iodine status of a population can be assessed by parameters such as Total Goiter Rate (TGR), Maternal urinary iodine concentration (MUIC), thyroglobulin levels in school-aged children, and neonatal thyroid stimulating hormone (TSH) levels. The neonatal thyroid has a low iodine content compared to the adult thyroid, and hence neonatal iodine turnover is much higher, especially in case of iodine deficiency. Consequently it has been assumed that the neonatal thyroid is extremely sensitive to iodine deficiency [2]. Assessment of iodine status in a population using MUIC and neonatal TSH concentrations is considered complementary [3]. However, the correlation between the two has been sparsely evaluated in the Indian context.

Recent estimates from surveys indicated that the median UIC (urinary iodine concentration) of the Indian population was 154 µg/L [4]. While iodine deficiency still persists in many parts of the country, iodine excess has recently been documented in a few studies from Delhi [5,6]. Thus, we aimed at assessing the correlation, if any, between MUIC and neonatal TSH levels, and to study the current iodine status in a group of mother-infant dyads.

Methods

This study was performed in a tertiary care center in New Delhi, India between November 2015 and November 2016. The study protocol was approved by Institutional Ethics Committee. Term healthy neonates weighing >2500 g and their mothers were included. Mothers who were hypothyroid, had autoimmune disease (diagnosed as anti TPO antibody positive), on antithyroid medication, requiring intensive postpartum care or had blood stained urine were excluded. The details of the age of mothers, parity, the type of salt used in their household were collected by verbal information. The antiseptic used during delivery was recorded.

Neonatal TSH levels were assessed using Dried blood

spot (DBS) collected by heel prick method from newborns between 24-48 hours after birth, as a part of an ongoing newborn screening project (NBS). It was ensured that the neonates were not exposed directly to povidone iodine. Neonatal TSH values >10 mIU/L (whole blood units) were excluded as it fell into the ambiguous zone. Simultaneously spot urine samples were collected from their mothers after obtaining informed and written consent. Spot urine samples of mothers processed in the postpartum period (Day 1-Day 7) whose neonates had TSH values >5 mIU/L were considered as case group, whereas those from postpartum mothers whose neonates had TSH values ≤5 mIU/L were considered as control group. Spot urine samples from 114 healthy pregnant mothers were also collected at term gestation. This group was considered after the study was initiated as the initial results were contrary to those envisaged in the original hypothesis, and to check whether the results of the MUIC could be related to use of povidone iodine during delivery.

Cut-offs and recommendations of the procedures to be followed were adopted from guidelines released by WHO [7]. According to WHO, the proportion of neonates with TSH values >5 mIU/L in whole blood is proportional to the degree of iodine deficiency during pregnancy. When a sensitive TSH assay is performed on the samples, <3% frequency of TSH values >5 mIU/L indicates iodine sufficiency in a population.

The cut-off values to define a population having iodine sufficiency are median urinary iodine concentration between 100-199 µg/L in children, 150-249 µg/L in pregnant women and ≥100µg/L in lactating women. Iodine insufficiency in postpartum and pregnant mothers was considered at urinary iodine levels <100 µg/L and <150 µg/L, respectively; iodine levels between 250-499 µg/L were considered as 'above requirements' in pregnant mothers; and iodine excess was considered at levels ≥300 µg/L and ≥500 µg/L during postpartum and pregnancy period, respectively.

TSH was measured by time resolved fluro-immunoassay on the Genomic screening processor (Perkin Elmer Life Sciences, Turku Finland). The limit of detection of the assay was 2 µU/L and the coefficient of variation <5%. The iodine concentration in urine was measured by the Wet Digestion method with internal quality control, and the results were expressed as µg/L.

The sample size of 400 mother neonatal dyads was estimated with the power of 90% and alpha error of 5%, based on a previous study which established the correlation between neonatal TSH and MUIC (r = -0.67) [8].

Statistical analysis: The analysis was done using STATA 11 software. Chi-square test was used to identify the relationship between neonatal TSH status (≤ 5 or >5 mIU/L) and MUIC. One way ANOVA with post-hoc Tukey HSD (Honest significant difference) test was used to compare TSH levels in iodine deficient, sufficient and excess group based on urinary iodine levels. The Spearman rank test was used to identify the correlation between MUIC and neonatal TSH levels.

RESULTS

The total number of deliveries in our institution during the study period was 12785. The number of neonates having TSH between 5.1-10 mIU/L was 1555 (12.1%). After the maternal and neonatal exclusion factors, 1050 neonates were found eligible. Out of these, urinary samples from a convenient sample of 400 mothers of cases and 144 mothers of controls were collected.

The general characteristics of the mothers and the neonates in the two groups are detailed in ***Table* I**. Iodized salt consumption was noted in 97% of the population. Povidone iodine (5%) was used as an antiseptic for conducting deliveries in all the patients. The mean maternal urinary iodine levels were 223 µg/L and 240 µg/L in cases and controls, respectively. The proportion of mothers with iodine insufficiency as well as iodine excess were significantly higher in cases than controls (***Table* I** and ***Fig*. 1**). When mothers were grouped based on urinary iodine levels as iodine deficient, sufficient and excess, it was found that mothers excreting insufficient (<100 µg/L) and excess iodine (≥300 µg/L) had significantly increased neonatal TSH levels than iodine sufficient group (P<0.001). It was also found that iodine excretion in urine was significantly lower in mothers who consumed non-iodized salt (P=0.03). The mode of delivery had a

TABLE I COMPARISON OF PARAMETERS BETWEEN CASES AND CONTROLS (N=544)

	Neonatal TSH Levels	
	≤5 mIU/L (n=144)	*>5mIU/L (n=400)*
*Maternal age (y)**	26.3 (4.5)	25.8 (3.9)
Primipara#	49 (34)	176 (44)
Caesarian delivery#	38 (26.4)	98 (24.5)
*Maternal UIC (µg/L)**	223 (78.3)	240 (103.5)
Male gender;*n (%)*	74 (51.3)	221 (55.3)
*Birth weight (g)**	2818 (475)	2921 (314)
Maternal UIC <100 µg/L#	8 (5.5)	40 (9.8)
Maternal UIC ≥300 µg/L#	60 (41.7)	217 (54.3)

*Cases=TSH >5 mIU/L; Controls = TSH <5 mIU/L; UIC: urinary iodine concentration; *Mean (SD); #n (%).*

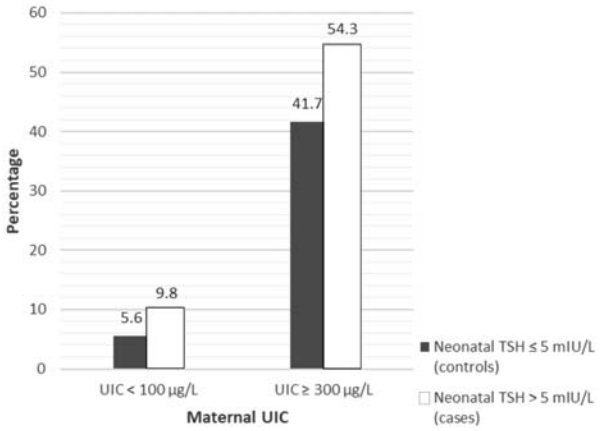

FIG. 1 *Maternal iodine deficiency and excess in the enrolled neonates.*

significant association (P <0.001) with MUIC, with levels being higher in mothers who underwent caesarean section. There was no significant correlation observed between neonatal TSH levels and MUIC.

Among the pregnant mothers, the mean urinary iodine level was 242.8 (74.8) µg/L. Iodine insufficiency (UIC <150 µg/L) was present in 13.6% whereas more than adequate urinary iodine (UIC ≥250 µg/L) was present in 65.3%.

DISCUSSION

In this cross-sectional hospital-based study, we observed that maternal iodine insufficiency as well as excess was more frequent among neonates with TSH >5 mIU/L than those with level ≤5 mIU/mL. Mean neonatal TSH was also higher in those postpartum mothers who excreted insufficient or excess iodine. There was no correlation observed between MUIC and neonatal TSH. 65.3% pregnant mothers had more than adequate iodine in their urine; insufficiency was observed in only 13.6% of the pregnant mothers.

The finding of iodine excess in our study is in consonance with the data from school-going children of upper socioeconomic strata [6], which demonstrated that 83% of the children had urinary iodine concentration (UIC) ≥300 µg/L. Grewal, *et al*. [5], also reported trimester specific UIC of 150 pregnant women to be in the range of 304 µg/L, and 77.4% had UIC ≥250 µg/L. Both the groups attributed the finding to improvement in the implementation of universal salt iodization and additionally other non-salt sources of iodine.

According to WHO, the proportion of neonates with TSH values >5 mIU/L in whole blood is proportional to the degree of iodine deficiency during pregnancy. Elevated neonatal serum TSH concentration may indicate insufficient supply of thyroid hormones to the developing fetal brain, and is therefore the only measure that allows prediction of brain damage due to iodine deficiency [2]. The cutoff of neonatal TSH >5 mIU/L used in our study has been suggested to be a good discriminator for severe iodine deficiency in the population; though, reports from certain areas of mild deficiency suggest it to be questionable.

The reasons for elevation of TSH in iodine deficiency are implicit. However, elevation of neonatal TSH levels in iodine excess group is contrary to the popular belief; however, it could be explained by a mechanism called Wolff-Chaikoff effect [9]. Both iodine excess and deficiency causing a raised neonatal TSH level might have resulted in a lack of correlation between MUIC and neonatal TSH levels.

The main strength of this study was the identification of recent tilt in the axis of iodine status in females, and the same finding even in pregnant mothers who were not exposed to povidone iodine. This emphasizes the fact that closer surveillance on both salt and non-salt sources of iodine should be done. Its long term implication has not been evaluated in terms of neonatal cognitive domain and general health. Extrapolation from adult data from India [10,11] suggests increasing autoimmunity and anti-TPO antibody positivity, which may have an impact on long-term neonatal health.

There were few limitations of this study. First, the collection of neonatal blood samples between 24-48 h may not be the best strategy for evaluating the TSH status. The proportion of population consuming iodized salt was recorded but we did not measure the content of iodine in salt samples on the basis of recall. Re-estimation of urinary iodine beyond the postpartum period or analysis of other thyroid parameters like thyroglobulin was also not performed in this study. As iodine is also excreted in breast milk, MUIC may lead to underestimation of iodine intake.

We conclude that neonatal TSH levels have no direct relationship with maternal urinary iodine levels; iodine insufficiency as well as excess seem to be higher among mothers of newborns with high (>5 mIU/L) TSH levels at 24-48 hours. Though iodine deficiency was still present in a proportion of the study samples, the looming burden of the excess is indeed a matter of concern. Few countries [12,13] have already entered the post-iodization era and report iodine excess. Further large scale multicentric studies across geographical zones, including coastal and mainland areas, are required along with robust parameters of assessment such as thyroglobulin and iodine content

WHAT IS ALREADY KNOWN?

- The iodine status of the nation is not yet sufficient and intensive universal salt iodization programs are in place to address this issue.

WHAT THIS STUDY ADDS?

- The proportion of mothers with iodine insufficiency as well as excess is more in newborns with deficient thyroid status (TSH >5 mIU/L).

of the salt, relationship between maternal iodine and neonatal thyroid status.

Contributors: HS, SK, BKT: conceived the idea of the project; SY,RG: were involved in management; AJ, RB: was responsible for the laboratory an alysis; SG: managed the mothers antenatally; All the authors have contributed to manuscript writing and approved the final version.
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REFERENCES

1. Pandav CS, Yadav K, Srivastava R, Pandav R, Karmarkar MG. Iodine deficiency disorders (IDD) control in India. Indian J Med Res. 2013;138:418-33.
2. Vandevijvere S, Coucke W, Vanderpas J, Trumpff C, Fauvart M, Meulemans A, *et al.* Neonatal thyroid-stimulating hormone concentrations in Belgium: A useful indicator for detecting mild iodine deficiency? PLoS One. 2012;7:e47770.
3. Vanderpump MPJ, Lazarus JH, Smyth PP, Laurberg P, Holder RL, Boelaert K, *et al*. Iodine status of UK schoolgirls: A cross-sectional survey. Lancet. 2011;377:2007-12.
4. Rah JH, Anas AM, Chakrabarty A, Sankar R, Pandav CS, Aguayo VM. Towards universal salt iodisation in India: Achievements, challenges and future actions. Matern Child Nutr. 2015;11:483-96.
5. Grewal E, Khadgawat R, Gupta N, Desai A, Tandon N. Assessment of iodine nutrition in pregnant north Indian subjects in three trimesters. Indian J Endocrinol Metab. 2013;17:289-93.
6. Marwaha RK, Tandon N, Desai A, Kanwar R, Mani K. Iodine nutrition in upper socioeconomic school children of Delhi. Indian Pediatr. 2010;47:335-8.
7. World Health Organization. A Guide for Programme Managers. Assessment of Iodine Deficiency Disorders and Monitoring their Elimination. Geneva: World Health Organization; 2007.
8. Hamza R, Youssef A, Mouharam W, Danasoury AEl. Maternal and neonatal iodine nutrition in Cairo. Internet J Pediatr Neonatol. 2007;8:2.
9. Wolff J, Chaikoff IL. Plasma inorganic iodide as a homeostatic regulator of thyroid function. J Biol Chem. 1948;174:555-64.
10. Usha Menon V, Sundaram KR, Unnikrishnan AG, Jayakumar RV, Kumar NV. High prevalence of undetected thyroid disorders in an iodine sufficient adult south Indian population. J Indian Med Assoc. 2009;107:72.
11. Marwaha RK, Tandon N, Karak AK, Gupta N, Verma K, Kochupillai N. Hashimoto's thyroiditis: Countrywide screening of goitrous healthy young girls in postiodization phase in India. J Clin Endocrinol Metab. 2000;85: 3798-802.
12. Katagiri R, Yuan X, Kobayashi S, Sasaki S. Effect of excess iodine intake onthyroid diseases in different populations: A systematic review and meta-analyses including observational studies. PLoS One. 2017;12:p.e0173722.
13. Bürgi H. Iodine excess. Best Pract Res Endocrinol Metab. 2010;24:107-15.