Trimester-specific Thyroid-stimulating Hormone: An Indian Perspective

Guidelines for Trimester-specific Thyroid-stimulating Hormone

Current guidelines on the management of thyroid disorders during pregnancy strongly recommend the establishment of population-based trimester-specific reference ranges for thyroid-stimulating hormone (TSH).[1] This is an important aspect of clinical endocrinology, as the reference range directly impacts clinical decision-making and institution of therapy. Population-based reference ranges are expected to be calculated based on data of healthy pregnant women, with no personal or family history of thyroid dysfunction, no visible or palpable goiter; history of thyroid disease, with optimal iodine intake; and negative thyroid peroxidase antibody status. In accordance with the International Federation of Clinical Chemistry,[2] reference intervals should extend from the 2.5th to 97.5th percentile.[3,4] While standard investigations require a minimum of 120 measurements for the establishment of normal ranges, thyroid function tests need a minimum of 400 individual measurements for validation of healthy reference ranges.[5] This is due to the high interindividual variability and skewness of data.

Variability of Thyroid-stimulating Hormone

Factors to be considered in the interpretation of TSH in pregnancy are preanalytical factors such as gestational age, presence of thyroid antibodies, iodine status, multiple pregnancies, ethnicity, and time of collection of TSH sample. Serum human chorionic gonadotropin concentrations tend to be higher, and TSH concentrations tend to be lower in women with multiple pregnancies.[6]

Circadian TSH rhythm has been observed in pregnant women as well as in nonpregnant women, with this circadian variation persisting in the second and third trimesters. Thus, failure to standardize collection time may interfere with the results and interpretation of the tests.[7]

Different immunoassays result in different TSH values. In general, the 97.5th percentile of TSH for the first trimester is located in two groups: according to the Architect, Beckman, and Immulite platform, it is about 3.0 mIU/L, while according to Centaur and Roche, it is close to 4 mIU/L.[6]

Indian Data

Over the past few years, Indian endocrinologists have worked hard to identify center-based or population-based trimester-specific data for TSH. Perhaps the first effort in this direction, by Kumar *et al*., from New Delhi, is available online only in abstract form.[8] The seminal effort of 2008 by Marwaha *et al*., from New Delhi, continues to enjoy sempiternal relevance.[9] This work has been expanded upon by Sekhri *et al*. from the same institute[10] and complemented by authors from Haryana, Maharashtra, and Manipur.[11-13] A well-conducted study from Bengal has also been published in 2014.[14] However, as this uses ELISA techniques to measure thyroid function tests, its relevance to modern thyroidology is debatable.

Heterogeneity in Design and Results

In this editorial, we compare the data from the six relevant published studies on trimester-specific ranges for thyroid function tests [Tables 1-3]. Broadly speaking, these studies have similar inclusion and exclusion criteria. Some are longitudinal in nature, whereas others are cross-sectional. Some studies rely on dietary history to assess iodine sufficiency, whereas others measure urinary iodide concentration to prove the same. Ultrasonography and thyroid antibodies screening are done by some, but not all authors for exclusion of nonhealthy participants. Most, authors mention the details of their kits, including sensitivity, coefficients of variation, nonpregnant reference ranges, and manufacturer identity. Some choose to report 5th and 95th percentile cutoffs, others prefer 2.5th and 97.5th percentiles, and yet others mention both. All mention mean values of thyroid function tests, whereas only four report median values. All but two measure free T3 and free T4 [Table 4]. This heterogeneity makes it difficult to compare these data sets. An eyeball analysis of the Indian data suggests that there is high heterogeneity between the various data sets. The lowest reference ranges are reported from Manipur and the highest from New Delhi. Rohtak and Nagpur reference ranges fall between those reported from Manipur and the national capital.

Need for Harmony

Reference ranges are of two types: health associated and decision based. The data discussed above are health associated, as it communicates thyroid function status of healthy Indian women. This does not necessarily translate into decision-making utility.[15] To do so, we need more robust data from all parts of the country, which can be analyzed together. We appreciate the opinion of Jebasingh *et al*., who highlight the multifaceted ethnic makeup of our country.[13] However, in a situation where limited funds are available, it makes sense to harmonize not only assays but also research methodology.[16,17] This will help create a pan-India reference range for thyroid function tests not only in pregnancy[18] but also in other age groups.[15,19,20] These can be used to inform accurate and appropriate clinical decision-making throughout the country.

Table 1: Indian trimester-specific ranges for free triiodothyronine

Author	City	T1					T2					T3					Nonpregnant reference ranges		Unit
		n	LRL	Mean	Median	URL	*n*	LRL	Mean	Median	URL	*n*	LRL	Mean	Median	URL	LRL	URL	
Kumar *et al*. (2003)[6]	New Delhi	124	-	1.85*	-	5.86*	124	1.7*	2.47*	-	4.3	124	0.4*	1.82*		3.9*	-	-	nmol/L
Marwaha *et al*. (2008)[7]	New Delhi	107	1.92	4.36	4.4	6.65	137	3.2	4.34	4.3	5.7	87	3.3	4.15	4.1	5.18	3.7	7.2	pM/L
Sekhri *et al*. (2016)[8]	New Delhi	86	3.1	-	4.36	6.35	86	2.39	-	4.09	5.12	86	2.57	-	4.00	5.68	3.7	7.2	pM/L
Mankar *et al*. (2016)[9]	Nagpur	50	0.29	2.046	-	3.1	50	0.27	2.045	-	3.34	50	0.24	4.96	-	3.61	-	-	ng/100 mL
Rajput *et al*. (2016)[10]	Rohtak	301	2.53	3.36	3.28	4.54	308	2.0	3.21	3.01	4.73	374	2.01	2.92	2.86	4.10	2.3	4.2	pg/mL
Jebasingh *et al*. (2016)[11]	Imphal	109	88.2805*	124.11*	119.17*	176.80*	148	102.24*	159.25*	152.94*	233.27*	118	88.46*	153.20*	154.42*	205.50*	60*	181*	ng/dL

*TT3: Total T3. LRL: Lower reference limit, URL: Upper reference limit, T3: Triiodothyronine

Table 2: Indian trimester-specific ranges for free thyroxine

Authors	City	T1					T2					T3					Nonpregnant reference ranges		Unit
		n	LRL	Mean	Median	URL	*n*	LRL	Mean	Median	URL	*n*	LRL	Mean	Median	URL	LRL	URL	
Kumar *et al*. (2003)[6]	New Delhi	124	-	164.50*	-	-	124	92.2*	165.80*	-	252.8*	124	108.2*	159.90*	-	219.20*	-	-	nmol/L
Marwaha *et al*. (2008)[7]	New Delhi	107	12	14.9	14.46	19.45	137	9.48	14.0	13.4	19.58	87	11.3	13.76	13.28	17.71	12.0	23.0	pM/L
Sekhri *et al*. (2016)[8]	New Delhi	86	9.81	-	13.5	18.53	86	8.52	-	12.28	19.43	86	7.39	-	11.40	18.28	12.0	23.0	pM/L
Mankar *et al*. (2016)[9]	Nagpur	50	01	4.39	-	2.2	50	0.45	4.89	-	2.24	50	0.47	5.03	-	5.1	-	-	ng/100 mL
Rajput *et al*. (2016)[10]	Rohtak	301	0.88	1.29	1.25	1.78	308	0.91	1.21	1.18	1.78	374	0.83	1.21	1.15	1.73	0.89	1.76	ng/mL
Jebasingh *et al*. (2016)[11]	Imphal	109	6.49*	9.98*	6.49*	13.75*	148	7.9*	11.47*	11.47*	16.06*	118	7.77*	11.48*	11.80*	15.30*	4.50*	12.60*	ng/dL

*TT4: Total T4. LRL: Lower reference limit, URL: Upper reference limit, T4: Thyroxine, T3: Triiodothyronine

Table 3: Indian trimester-specific ranges for thyroid stimulating hormone

Authors	City	T1					T2					T3					Nonpregnant reference ranges		Unit
		n	LRL	Mean	Median	URL	*n*	LRL	Mean	Median	URL	*n*	LRL	Mean	Median	URL	LRL	URL	
Kumar *et al*. (2003)[6]	New Delhi	124	-	1.2	-		124	0.1	2.12	-	5.5	124	0.5	3.30	7.6	-	-	-	μIU/mL
Marwaha *et al*. (2008)[7]	New Delhi	107	0.6	2.42	2.1	5.0	137	0.435	2.49	2.4	5.78	87	0.74	2.6	2.1	5.7	0.27	0.42	μIU/mL
Sekhri *et al*. (2016)[8]	New Delhi	86	0.09	-	1.89	6.65	86	0.51	-	2.31	6.66	86	0.91	-	2.26	4.86	0.27	4.2	μIU/mL
Mankar *et al*. (2016)[9]	Nagpur	50	0.24	1.65	-	4.17	50	0.78	2.59	-	5.67	50	0.47	2.77	-	5.78	-	-	μIU/mL
Rajput *et al*. (2016)[10]	Rohtak	301	0.37	1.63	1.40	3.69	308	0.54	1.79	1.74	4.47	374	0.7	1.21	1.15	4.64	0.35	5.5	μIU/mL
Jebasingh *et al*. (2016)[11]	Imphal	109	0.21	1.06	1.08	1.82	148	0.71	1.23	1.23	1.71	118	0.7	1.25	1.23	1.93	0.35	5.5	μIU/mL

LRL: Lower reference limit, URL: Upper reference limit, T3: Triiodothyronine

Table 4: Research methodology

Authors	Design	Iodine sufficiency	Thyroid antibody status	Thyroid ultrasonography	Details of kit	Percentile cutoffs	Calculated average	T3, T4 estimation
Kumar *et al*. (2003)[6]	Longitudinal	Not mentioned	Not mentioned	Not mentioned	Not described	5th, 95th percentile mentioned for two trimesters	Mean + median	Total
Marwaha *et al*. (2008)[7]	Cross-sectional	Iodized salt intake + urinary iodide estimation	Assessed	Done	Described in detail	2.5th, 97.5th percentiles	Mean + median	Free
Sekhri *et al*. (2016)[8]	Longitudinal	Iodized salt intake + urinary iodide estimation	Assessed	Not done	Described in detail	2.5th, 97.5th percentiles	Mean + median	Free
Mankar *et al*. (2016)[9]	Cross-sectional	Urinary iodine excretion	Not assessed	Not done	Name mentioned	5th, 95th percentiles	Mean	Free
Rajput *et al*. (2016)[10]	Cross-sectional	Iodized salt intake	Assessed	Not done	Described in detail	2.5th, 97.5th and 5th, 95th percentile both	Mean + median	Free
Jebasingh *et al*. (2016)[11]	Cross-sectional	Iodized salt intake	Not assessed	Not done	Described in detail	5th, 95th percentiles	Mean + median	Total

Current Recommendations

Due to ethnic differences and geographical variations in populations, 2011 ATA and 2012 Endocrine Society guidelines recommended that the normal range of TSH should be determined locally for each population. The recommended upper TSH value in the first trimester in both the 2011 and the 2012 guidelines was 2.50 mU/L[21,22] and 3.00 mU/L in second and third trimester. In the latest 2017 ATA thyroid and pregnancy guidelines, 19 studies published upper normal TSH limits (defined as the 97.5th percentile) ranging from 2.15 mU/L to 4.68 mU/L. A universal TSH cutoff distinguishing the upper range of normal from the lower range of abnormal does not exist.

The 2017 ATA thyroid and pregnancy guidelines recommend that an upper reference limit (URL) of 4.0 mU/L can be used if internal or transferable pregnancy-specific reference ranges of TSH are not available. However, a review of the 19 studies referenced in the 2017 ATA thyroid and pregnancy guidelines reveals that only 5 of 19 of the papers cited, reported an upper limit of normal ≥4.0 mU/L. Out of five largest studies cited (each including more than 5000 pregnant women), only one reported an upper limit of normal exceeding 3.5 mU/L. To ensure that most women with subclinical hypothyroidism are appropriately diagnosed, we conclude that recent 2017 recommendation of ATA of a revised URL for TSH of 4.0 mU/L is high and should instead be 3.0 mU/L in the first trimester and 3.5 in second and third trimester. These values should be used in India, till we are able to generate more nationally representative data for trimester-specific TSH values.

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Conflicts of interest

There are no conflicts of interest.

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