



Thyroid-Stimulating Hormone Reference Ranges in Early Pregnancy: Possible Influence of Iodine Status

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In 2016, the American Thyroid Association (ATA) released new guidelines for diagnosing and managing thyroid diseases during pregnancy and the postnatal period [1]. The most important difference from the previous guidelines published in 2011 was the definition of the upper limit of trimester-specific thyroid-stimulating hormone (TSH) reference ranges during pregnancy. For example, the upper TSH limit during the first trimester of pregnancy was 2.5 mIU/L according to the 2011 ATA guidelines, but the 2016 ATA guidelines recommended using population-based trimester-specific reference limits, the values of which are usually much higher than those of previous guidelines. Those changes were based on large-scale cohort studies in several countries that have been recently published [2-6]. The substantial population differences in TSH reference ranges during pregnancy might be explained by differences in ethnicity, geographic location, iodine intake, body size, thyroid autoantibody positivity, and the TSH assays used for analysis [7].

The TSH reference interval was defined by 95% confidence limits of the log-transformed values of at least 120 rigorously screened normal euthyroid volunteers, according to the National Academy of Clinical Biochemistry (NACB). Normal euthyroid subjects were defined as those with no detectable thyroid peroxidase antibody (TPOAb) or thyroglobulin antibody, no personal or family history of thyroid dysfunction, no visible or palpable goiter, and no use of any medications affecting thyroid function except estrogen [8]. However, the NACB guideline does not consider the iodine intake of the population when defining the

reference population for TSH measurements. Nonetheless, many guidelines recommend using populations with adequate iodine intake to define TSH reference ranges [1,9,10]. Both iodine deficiency and iodine excess can be associated with reduced thyroid function [11], and these possibilities should be considered as an important parameter for defining population-based trimester-specific reference ranges of TSH.

In this issue of *Endocrinology and Metabolism*, Castillo et al. [12] determined the thyroid hormone reference range of pregnant women in Chile. They recruited 1,022 pregnant women in their first trimester, checked their thyroid function and TPOAb status, and used NACB guidelines to select 670 subjects as the reference population. The reference range of TSH was 0.13 to 5.37 mIU/L, with a median level of 1.88 mIU/L. The reference upper limit proposed by the manufacturer of the assay for TSH for non-pregnant women was 4.2 mIU/L and the upper limit suggested by the 2011 ATA guideline was 2.5 mIU/L. Therefore, the prevalence of subclinical and/or overt hypothyroidism was 34.8%, 10.4%, or 5.7% according to the reference range suggested by the 2011 ATA guideline, the manufacturer's reference, and the present study, respectively (shown in Fig. 3 of Castillo et al. [12]). This discrepancy means that the number of pregnant women to be treated by levothyroxine varies significantly according to the choice of the TSH reference range. Levothyroxine is a quite safe medication for pregnant women, and some clinicians still follow the 2011 ATA guideline, which defines the TSH reference as 2.5 mIU/L due to the fear of under-

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treatment. However, several recent studies have repeatedly shown that a TSH level of 2.5 mIU/L, or even the kit manufacturer's reference range for TSH, might be too strict to be used as an indicator for levothyroxine treatment, because no definitive benefit of levothyroxine treatment was reported using those TSH reference values.

Castillo et al. [12] also evaluated the iodine status of pregnant women in Chile. They stated that the Chilean universal salt iodine fortification program started in 1979, and required each kilogram of salt to be fortified with 100 µg of iodine (100 ppm). In 2000, very high levels of iodine were found in school-aged children, so the level of iodine was reduced to 40 ppm. The median urinary iodine concentration was 173.45 µg/L (interquartile range, 108.11 to 249.35), reflecting adequate iodine status according to World Health Organization recommendations [13]. Nonetheless, some proportion of the population still showed iodine deficiency or more than adequate iodine status, as shown in Fig. 2 of the paper by Castillo et al. [12]. Those historical changes in the iodine fortification program and/or current iodine status might explain why the population of their study showed a right-shifted distribution of serum TSH during pregnancy.

It is crucial to establish population-based trimester-specific reference ranges to identify and treat hypothyroidism in pregnant women. However, the effects of iodine intake and the optimal level of during pregnancy remain to be determined.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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REFERENCES

- Alexander EK, Pearce EN, Brent GA, Brown RS, Chen H, Dosiou C, et al. 2017 Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017; 27:315-89.
- Mannisto T, Surcel HM, Ruokonen A, Vaarasmaki M, Pouta A, Bloigu A, et al. Early pregnancy reference intervals of thyroid hormone concentrations in a thyroid antibody-negative pregnant population. *Thyroid* 2011;21:291-8.
- Medici M, de Rijke YB, Peeters RP, Visser W, de Muinck Keizer-Schrama SM, Jaddoe VV, et al. Maternal early pregnancy and newborn thyroid hormone parameters: the Generation R study. *J Clin Endocrinol Metab* 2012;97:646-52.
- Li C, Shan Z, Mao J, Wang W, Xie X, Zhou W, et al. Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? *J Clin Endocrinol Metab* 2014;99:73-9.
- Bestwick JP, John R, Maina A, Guaraldo V, Joomun M, Wald NJ, et al. Thyroid stimulating hormone and free thyroxine in pregnancy: expressing concentrations as multiples of the median (MoMs). *Clin Chim Acta* 2014;430:33-7.
- Laurberg P, Andersen SL, Hindersson P, Nohr EA, Olsen J. Dynamics and predictors of serum TSH and fT4 reference limits in early pregnancy: a study within the danish national birth cohort. *J Clin Endocrinol Metab* 2016;101:2484-92.
- Medici M, Korevaar TI, Visser WE, Visser TJ, Peeters RP. Thyroid function in pregnancy: what is normal? *Clin Chem* 2015;61:704-13.
- Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 2003;13:3-126.
- Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J* 2014;3:76-94.
- De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:2543-65.
- Shi X, Han C, Li C, Mao J, Wang W, Xie X, et al. Optimal and safe upper limits of iodine intake for early pregnancy in iodine-sufficient regions: a cross-sectional study of 7190 pregnant women in China. *J Clin Endocrinol Metab* 2015;100:1630-8.
- Castillo C, Lustig N, Margozzini P, Gomez A, Rojas MP, Muzzo S, et al. Thyroid-stimulating hormone reference ranges in the first trimester of pregnancy in an iodine-sufficient country. *Endocrinol Metab* 2018;33:466-72.
- World Health Organization. Assessment of iodine deficiency disorders and monitoring their elimination. 3rd ed. Geneva: World Health Organization; 2007.