Reviewer's report

Title: Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study

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Reviewer: Thomas Vulsma

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Dr. Kapelari and coworkers studied a large hospital-based group of children and adolescents (1 day – 18 years) to establish age-specific reference intervals for the common determinants of thyroid function (the plasma concentrations of TSH, FT4 and FT3). In principle a very useful addition to the scarce data in the literature. The new data were compared with the reference intervals published since 1995.

Comments:

1. Introduction (background): neonatal CH screening in most countries is wishfull thinking; only developed countries have such screening programs. [Minor]

2. Introduction: the plasma (F)T3 concentration does not directly reflect hormone production by the thyroid. Most of the circulating T3 is produced in the peripheral tissues. [Minor]

3. Methods: it is not clear whether the investigators just collected existing laboratory data (originally meant for patient care), or used existing serum samples of pediatric patients (meant to measure thyroid function determinants just for the study), or took blood samples just for study purposes. [Major]

4. Methods: The subjects are in fact patients. I have no problem with the exclusion criteria, but I like to know which disease entities were present in the included patients. Beware of non-thyroidal illness. Some of the easily available determinants of health status in children are weight and height. Overweight and obesity, as well as underweight and anorexia, influence thyroid function determinants (as noted in the introduction). In general, height and weight measurements of pediatric patients are available, as are the auxologic data of the general population. Growth data of the included patients should be analyzed to verify their health status. [Major]

5. Methods: The authors mention 414 primarily healthy subjects, being a subgroup of the hospital-based population of 2194 children and adolescents. Children are patients (having a disease, or at least having signs and symptoms), or not (being healthy, or not aware of having a disease). A hospital-based healthy population is peculiar. For healthy children ethical rules are different! [Major]

6. Methods: 1495 patients had at least one serum sample taken; what about the other 699 patients? 665 patients with a thyroid condition were excluded. Subtracted from which number? This is an unusual high percentage thyroid
problems among pediatric patients. Explanation? [Major]

7. Methods: Mention the reference ranges (for adults) provided by the manufacturer Bayer, especially for comparison with assays from other manufacturers. [Minor]

8. Results: TSH: I am confused about the ‘longitudinal subgroup (n=32)’ How old were these children? For what reason their TSH was measured initially? What was the cause of the elevated TSH levels? Were anti-thyroid antibodies measured? Which TSH measurements are included (all, or only the normalized ones?). What was the reason not to exclude these subjects? [Major]

9. Discussion: Reference intervals meant for healthy children and adolescents, but derived from a hospital based population. The authors have to prove their validity first. And not only by exclusion of the patients with a well-known thyroid problem. [Major]

10. Discussion: Mention the adult reference ranges for the Advia Centaur assays, and compare them with those used in the literature, to demonstrate the method-dependance. (can be included in Table 6). [Minor]

11. Discussion: Mention the iodine status of Austria. [Minor]

12. Discussion: The longitudinal subgroup has nothing to do with producing reference ranges. Treatment depends on the clinical status of the patient, and etiology. Repeated measurement have nothing to do with the indication to treat (or not).[Major]

13. Discussion: The differences with literature data (Table 4-6) should be emphasized in the text. [Minor]

14. Figures: the numbers below the figures differ from the numbers of the corresponding legends! [Minor]

15. Figure 1 (and 3, 4, 5): the lines start at age zero, but definitely the first hours after birth are not included (postnatal TSH surge)! This should be mentioned in the text or in the legend. [Minor]

16. Figure 2: useless, confusing (see comment 8). [Major]

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests