**Reviewer’s report**

**Title:** Urinary iodine in early pregnancy is associated with subclinical hypothyroidism in Tianjin, China: an observational study

**Version:** 0 **Date:** 26 Sep 2016

**Reviewer:** Sun Lee

**Reviewer’s report:**

Summary: This is a cross-sectional study of assessment of UIC, thyroid function, and thyroid antibody status in 55 pregnant women with subclinical hypothyroidism and 66 euthyroid pregnant women in the first trimester (median gestational age of 10 weeks) in Tianjin, China.

Strength: Several measures assessing the subjects' thyroid status were measured, including full set of thyroid function tests, thyroid antibody status, as well as thyroid ultrasonography. Pregnancy-specific reference ranges for thyroid function tests developed specifically for this population was used.

Weakness: small sample size. Since a spot UIC was measured in a relatively small sample, it would be difficult to generalize the UIC findings in this study to the whole population of pregnant women in Tianjin, China.

1. In Methods - Subjects section, authors report that "women who took anti-thyroid drugs, iodine containing drugs or supplements" were excluded. Were the women who were taking thyroid medications such as levothyroxine or liothyronine also excluded? What are the specific iodine-containing drugs whose uses were assessed? Also, was there any assessment done regarding a recent IV contrast exposure, which contains excess amount of iodine?

2. There are some confusion in the designation of thyroid stimulating hormone. The initial abbreviation in methods section was TSH, but throughout the manuscript, TSH and sTSH are used interchangeable. Please unify.

3. In Methods - Ultrasonography section, authors report that thyroid volume was calculated using the "HWL" method. Is this an abbreviation? If so, please define the abbreviation. The method used to calculate thyroid volume should also have a citation of the literature describing the method.

4. In Results section, authors describe the comparison of serum thyroid function tests between subclinical and euthyroid women, however, the thyroid function tests are not presented. It would helpful to include the median(range) for TSH, FT4, and FT3 and the p-value for comparison between the group, possibly in Table 1.

5. In Discussion section, authors describe the physiological increase in demand for iodine requirements in pregnant women. In addition to increased clearance of iodine and increased
demand for thyroid hormone production, transplacental iodine transfer from pregnant woman to fetus, especially later in gestation, should also be included as one of the reasons for increased iodine requirement in pregnant women.

6. In Discussion section, authors state "As >90% of ingested iodine is ultimately excreted in the urine, urinary iodine concentration (UIC) is a good indicator of iodine nutritional status[21]." Here, it should be clarified that a spot UIC is a good indicator of recent iodine intake and a median UIC of a large sample can be used to assess population-level iodine nutritional status. Spot UIC cannot be used to assess an individual-level iodine nutritional status given its fluctuation based on recent iodine intake.

7. In Discussion, authors state "Our study showed the iodine nutrition status in early pregnancy in Tianjin was adequate, but since the median UIC was at the lower limit, the pregnant women still at risk of iodine deficiency as the pregnancy progressed." Please provide reasoning for this statement. If the pregnant women have adequate iodine intake now and if there is no evidence of significant change in iodine intake, why would these women be at a risk for later iodine deficiency?

8. In Discussion section, authors state "...pregnant women need an additional iodine intake of about 70 mcg/d with an estimated salt consumption of 6g/d." Please provide reference for this statement of estimated salt consumption of these women. Also, pregnant women may also obtain iodine through other food groups such as dairy products or meat/grain raised in iodine-rich soils, or seafood. If authors' intention for the above statement was to point out that pregnant women in Tianjin may not be taking adequate iodine, it would be helpful to have information regarding estimation of intake of other iodine-containing food group as well, as iodized salt may not be the only source of iodine.

9. In Discussion section, authors state "The Wolff-Chaikoff effect [25] may be responsible for this,..." However, this is not correct. The acute Wolff-Chaikoff effect is a protective mechanism against development of hyperthyroidism in the setting of iodine excess, and individuals without underlying thyroid abnormalities generally escape from the Wolff-Chaikoff effect within 24-48 hours. Development of subclinical or transient hypothyroidism in the setting of chronic iodine excess may rather be from the failure to escape from the Wolff-Chaikoff effect in susceptible individuals (Braverman LE, Thyroid 1994;4:351-6).

10. In Discussion section, authors state "It seems that more-than-adequate and excessive iodine rather than iodine deficiency is associated with SH in those with negative thyroid autoantibodies" and "...serological negative autoimmune thyroiditis is one of the important causes of SH with negative anti-thyroid autoantibodies in early pregnancy." These statements appear too much of a generalization based on the findings of this study. The sample size for the results that these statements are based on is very small at 10. Therefore, I would suggest revising the statement to limit the finding to this study, rather than making a general statement.

11. In Discussion section, authors state "Obesity and overweight are related to elevated TSH level[30], but whether contribute to idiopathic subclinical hypothyroidism in pregnancy and how to intervene remains to be investigated." I do not think the reference to elevated TSH in obesity
is appropriate here, as TSH elevation in obesity is though to be more of a physiologic response to increase resting energy expenditure, rather than subclinical hypothyroidism. Also, the degree of TSH elevation in these patients are generally mild, usually in the upper normal ranges. TSH is also seen to decrease back for more normal levels with weight loss.

12. In Conclusion section, authors state that "...but still at risk of iodine deficiency with pregnancy progressed." Please see my comments in #7.

13. In Conclusion section, authors state "...and the urine iodine concentration fluctuated according to the degree of urine concentrations," it should also be noted that the spot UIC only reflects recent iodine intake. Although authors report that the urine samples were pre-prandial samples in the Methods section, it is unclear if they were fasting samples or simply pre-prandial at any time of the day, in which case, UIC may still be affected by the recent iodine intake.

14. I think the limitations of this study briefly mentioned in the Conclusion section should be added to the Discussion section with a little more of explanation.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

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I am able to assess the statistics

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