Author’s response to reviews

Title: Effect of Mildly Elevated Thyroid-Stimulating Hormone during the First Trimester on Adverse Pregnancy Outcomes

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Author’s response to reviews:

Thank you for your reviews. We have revised the manuscript carefully following the comments. All the revised contents were highlight in this edition. We hope the revised edition would be more interesting. The responses to the referees are as follows:

Reviewer reports:

Jan Jiskra (Reviewer 1): The study aims to evaluate whether the effect of mild elevated TSH with concentrations between 2.5 and 4.0 mIU/l at the first trimester increased adverse pregnancy outcomes in TPOAb negative pregnant women. No differences in adverse pregnancy outcomes were observed between the mild elevated TSH group and the normal TSH group.

Main comments and limitations:

1. Why authors did not evaluate an incidence of pregnancy loos in the study? Probably, it is the most important adverse event during pregnancy. Repeated analysis with additional data about pregnancy loos must be performed before publication.
Response: Thank you very much for your comments. To evaluate an incidence of spontaneous abortion, we separately analyzed the data of incidence of spontaneous abortion among pregnant women in this hospital from June 2016 to June 2017 (added last paragraph in results). There were 94 women had spontaneous abortion. Among them, 25 subjects didn’t have thyroid function records. The remaining 69 subjects had median TSH 1.06 (0.58 - 1.66). Of the 1927 subjects with thyroid function records, the number of incidence of spontaneous abortion was 4 (2.5%), 58 (3.6%), 5 (3.4%) and 2 (9.5%) in subjects with TSH <0.1 mIU/L, 0.1 mIU/L ≤ TSH < 2.5 mIU/L, 2.5 mIU/L ≤ TSH <4.0 mIU/L and TSH ≥4.0 mIU/L, respectively (χ²=2.659, P=0.447). No statistic difference was observed in prevalence of spontaneous abortion among subjects with TSH <0.1 mIU/L, 0.1 mIU/L ≤ TSH <2.5 mIU/L and 2.5 mIU/L ≤ TSH <4.0 mIU/L (all P >0.05). These results suggested subjects with mild elevated TSH (2.5 mIU/L ≤ TSH <4.0 mIU/L) didn’t increase the incidence of spontaneous abortion.

2. Page 3, section "Methods", line 1-3 from the bottom: Women with TSH ≥4.0 mIU/L were treated with levothyroxine in this study. My question is how many women did achieve target TSH (<4.0 mIU/L) during pregnancy and when? Conversely, how many cases of initial TSH between 2.5–4.0 progressed to more than 4.0 mIU/L during pregnancy?

Response: In this study, we aimed to explore whether a mild elevated TSH with concentrations between 2.5 and 4.0 mIU/L at the first trimester increased adverse pregnancy outcomes in TPOAb negative pregnant women. Therefore, while analyzing adverse pregnancy outcomes, we excluded the data of subjects with TSH ≥4.0 mIU/L at the first trimester (most of these subjects have been treated with levothyroxine and reach TSH target). The second question is an interesting question. However, we didn’t collect all follow-up values of TSH among all subjects. At this time, we couldn’t answer this good question. We think it should be explored in future studies.

3. Section "Subjects": Did the women included in the study use iodine supplements? What is the iodine saturation in the area the study was performed?
Response : No, we didn’t examine the iodine in the study population. Universal Salt Iodisation (USI) was conducted in China from October 1994. In this area, the iodine in salt (mg/kg) was 34.1±3.6mg/kg[1]. According to the World Health Organization (WHO) guidelines, median urinary iodine (MUI) values for pregnant women between 149 and 249 μg/L are consistent with optimal iodine intake[2]. A study of more than 7000 pregnant Chinese women found that subclinical hypothyroidism and hypothyroxinemia were least common at the urinary iodine range of 150-249 μg/L[3]. According to the previous study[1], the iodine status in this area is adequate iodine intake (MUI concentration 166ug/L). In pregnant women, according Gu’s study in our province, the iodine saturation was 198.0 μg/L and the salt iodine concentration (15-35)mg/kg could fully meet the iodine nutritional needs[4]. So we didn’t use specific iodine supplements in the study population.

Minor remarks:

4. Page 3, section "Subjects", line 1: "Pregnant" instead of "Pregnancy"
Response: Revised (Subjects section, line 1, page 3).

5. Page 3, section "Methods", line 7 from the bottom: "free thyroxine" instead of "free thyroxine 4"
Response: Revised (Methods section, line 7 from the bottom, page 3).

6. Page 3, section "Methods", line 7 from the bottom: "were" instead of "was"
Response: Revised (Methods section, line 7 from the bottom, page 3).

7. Page 3, section "Methods", line 4-5 from the bottom: The reference range of normal TSH should be defined as 2.5 and 97.5th percentile of TPOAb negative women.
Response: Revised (Methods section, line 4-5 from the bottom, page 3).
8. Page 4, section: Methods", lines 5 and 13: "placental abruption" is doubled
Response: Thank you for your comments. The “placental abruption” is deleted (Methods section, line 5, page 4).

9. Page 4, section "Methods", line 3-5 from the bottom: "small and large for gestational age" - units are not present, it should be probably less than 10th percentile of length in centimeters and more than 90th percentile of length in centimeters.
Response: Thank you for your comments. The units are added (Methods section, line 3-5 from the bottom, page 4).

10. Page 6, section "Results", line 4 from the bottom: "(19.32(1.91)" - interquartile range is absent
Response: Revised (Results section, line 4 from the bottom, page 6).

11. Page 7, section "Results", line 1: probably "(16.46±3.11 vs 15.82±2.74)" instead of "(16.46(3.11) vs 15.82(2.74)"
Response: Revised (Results section, line 1, page 7).

Response: Thank you for your comment. The study by Springer et al. 2011 with upper 1st trimester TSH reference range of 3.67 mIU/L is cited (Discussion section, line 13, page 8).
Göksun Ayvaz (Reviewer 2):

1. In table 2 and in Results section, Pre-gestational BMI (kg/m²) of eTSH group should be given as 19.32(± SD) instead of 19.32(1.91). This should be corrected.

Response: All of these have been revised (Results section, line 4 from the bottom, page 6 and table 2).

2. To make it sure that the pregnant women don't have an autoimmune thyroid disease, presence of high Antithyroglobulin antibody levels should also be added into the exclusion criteria.

Response: It’s better to exclude the pregnant women with high anti-thyroglobulin antibody levels to make it sure that pregnant women don’t have an autoimmune thyroid disease. However, according to the national guidelines of the Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum in China, and similar to other studies, we haven’t routinely measure antithyroglobulin antibody levels in all pregnant women in the first trimester. The limitation on the amount of maternity insurance in our city also restricts this measurement.

References

