Author's response to reviews

Title: The impact of iodine supplementation and bread fortification in a mildly iodine deficient population of pregnant women in South Australia

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Version: 2 Date: 13 February 2013

Author's response to reviews: see over
Thank you for the thorough review of the manuscript. It was greatly appreciated and insightful.

**Reviewer 1**

*Abstract:* Abstract should be substantially revised according to reviewers’ suggestions. *Completed*

*Introduction:* More background should be given on iodine status of general population in the study area over the years if available.

There are no studies conducted in the South Australian population in relation to urinary iodine concentrations. We have included this comment in the background.

*Materials and Method:*

1. How many urine samples were provided from one subject? If all subjects (196) provided 5 samples the total number of sample should be 980.

126 women (64%) provided at least 3 samples, while 24 women (12%) provided only 1 sample, due to non-attendance at their scheduled antenatal appointments. Removal of these data points does not alter the results reported in the paper.

2. How much iodine is containing in the fortified bread?

Commercial production of bread was fortified with iodised salt rather than non-iodised salt and it was suggested by the Food Standards of Australia and New Zealand that this fortification would increase daily intake of iodine to 54 µg. There is no exact amount as addition of the amount of iodised salt to bread is at the discretion of the bakery. This has been added to the background information.

*Results*

1. The subjects should be divided into two groups according to the use of iodine-supplements. We think it was important to report the data comparing the three groups to establish no effect of other vitamins/supplements in altering iodine status. This acts as an important control group. Once this had been established, the data were grouped into two groups according to supplemental iodine use.

2. How much iodine is taking daily from iodine-containing supplements and fortified bread in the subjects?

It is predicted that 54 ug of iodine is derived from bread consumption and a iodine-containing multivitamin for pregnancy and lactation contains 75 ug and it is recommended that 2 multivitamins are taken per day. So overall women should have a UIC > 150 ug/ml. This has been placed in the methods.
3. The sample size is too small to evaluate gestational change of UIC. According to Figure 1 legend, the total number of collected urine sample is 278 (only 28% of 980 samples) and the percentages of subjects who provided urine sample are 47.1% at 12w, 38.7% at 18w, 26.6% at 30w, 18.8% at 36w and 10.7% at 6 postpartum months. It is better to combine all UIC samples in each gestational trimester and compare them. We agree with the reviewer that it would be beneficial to combine all UIC samples in each gestational trimester and compare – this was the analysis that was done and reported in the results section (paragraph 2). Data was then split to examine the impact of supplementation (paragraph 3, Figure 1).

4. L9-13
In which study group, UIC increased during and after pregnancy? Or are all UIC values of total subjects are combined?
UIC increased significantly over pregnancy in all women combined, regardless of supplementation (this is clarified in results section, paragraph 2).

5. L14-20
5-1. Iodine fortification of bread was introduced in October 2009 and the study period was from January 2009 to July 2010. The effect of bread iodine on UIC should be taken into evaluate the effect of iodine-containing supplements. The effect fortification relative to supplementation was negligible. The numbers of subjects were too few to do this analysis post hoc.
5-2. “The consumption of dietary supplements containing iodine significantly increased UIC --- “ This phrase is inaccurate and inappropriate. What is the evidence for this conclusion? The reviewer is correct and the conclusion has been reworded to say that the consumption of dietary iodine containing supplements was associated with a significant increase in the number of women achieving sufficient iodine (WHO recommended) levels.

6. L21-25
6-1. For lactating women the optimal UIC range as recommended by the WHO is 100µg/L and not 150µg/L.
In Fig 1 the median UIC value of postpartum women is more than 100µg/L and they are not iodine deficient.
The information we have reported was derived from the WHO, UNICEF and ICCIDD indicates 150-249 ug/ml are recommended for lactating women.

6-2. Median UIC values should be presented.
Agree. The values have been added to the text (text copied from manuscript below):

Urinary iodine concentrations increased significantly as pregnancy progressed (Friedman’s \( \chi^2 \)=12.974, \( p=0.005 \)). Post hoc comparisons indicated that UIC at 36 weeks (median=118) was significantly higher than UIC at 12 (median=73), 18 (median=68) and 30 weeks gestation (median=84; \( p<0.025 \) in all instances). UIC remained constant from 12 to 18 weeks, but was significantly higher at 30 weeks gestation compared to at 12 weeks.

7-1. Is the median UIC value of 82µg/L for overall subjects? Mention the mean (SD) gestational week.
Yes – this median value represents UIC for all subjects combined. The mean is gestational age is 23 (8) but this is not meaningful and so is not included.

Discussion
1. L22-24 "Charlton et al.3 reported that 35% of pregnant women used ----” This phrase is not consistent with the content of reference 3.
Corrected- wrong article cited for Charlton. New Charlton article included

2. L29-39 This sentence is too long. These facts are well known and established.
corrected

3. The pattern of change in UIC during and after pregnancy should be discussed.
We have included a paragraph in the discussion on this finding. See paragraph 4.

Figure 1: Revision is needed.
Done. Legend has also been altered in line with changes.

New legend:
Figure 1: Urinary iodine concentrations during pregnancy and 6 months postpartum according to the use of iodine-containing multivitamins, measured at 12 weeks (no iodine-containing multivitamins n=89, iodine-containing multivitamins n=76), 18 weeks (no iodine-containing multivitamins n=81, iodine-containing multivitamins n=79), 30 weeks (no iodine-containing multivitamins n=58, iodine-containing multivitamins n=62) 36 weeks (no iodine-containing multivitamins n=51, iodine-containing multivitamins n=60) and at 6 months postpartum (no iodine-containing multivitamins n=21, iodine-containing multivitamins n=17). Line and boxes represent the median and the inter-quartile range and whiskers represent the 95% confidence interval. *p< 0.05 between iodine supplement and no supplement group at 36 weeks (Mann Whitney U test); significant differences across gestation are represented by different alpha symbols (p<0.01).

Table 1: Subjects should be divided in two groups.
We do not agree – as stated above

Table 2: Median UIC with IQR and total number of subjects should be presented in each column.
Table 2 reports frequency data - Adding the median, IQR and subject numbers would be a repeat of the data presented in Figure 1.

Minor Essential Revisions

Introduction: Line 9, use "µg" instead of "micrograms"
done

Materials and Method: Urinary Iodine Concentration
1. Is the urine sample spot urine? Yes and added
2. This analytical method is already established and the detailed description is not necessary. Refined as requested

3. Calculate the inter- and intra-assay CV of iodine measurement. Completed

References: In Ref. 3 and 19, the published year “2010” is missing. Completed

Some important papers are neglected, such as Andersson M et al. J Nutr (2012), Glinoer D, Best Practice in Research in Clinical Endocrinology and Metabolism (2004) and Zimmermann MB, Endocr Rev (2009).

We have added 2 of the recommended papers

Reviewer 2

Minor essential revisions:
1. The phrase “iodine supplements” can be confusing and seems to imply pure potassium iodide or kelp supplements that these pregnant women are taking. Consider switching to the term “iodine-containing multivitamins”.

We have made this change

2. Methods, study participants: It is stated that 30% used dietary supplements that did not contain iodine. Is this 30% of the 47% who used any supplements, or of the total 196 women. I assume the latter, but please clarify in the text.

Yes – the reviewer is correct. This has been clarified in the text by adding in the actual numbers.

3. Results, third paragraph: The sentence stating that women who took non-iodine containing supplements were grouped together with those who did not take any iodine supplements based on the similarity of their UICs should be more clearly restated in the Methods section.

This has been corrected

4. Results, last paragraph: Although the overall median UIC is provided (82 mcg/L), please divide and also report the UICs for the women who were using iodine supplements vs. those who were not.

This has been added to the manuscript

The median UIC for pregnant women was 82 µg/L (with minimum-maximum 1-754 µg/L) indicating mild iodine deficiency. The consumption of iodine supplements was associated with a significantly higher UIC over pregnancy (median=89µg/L, minimum-maximum 1-754 µg/L) than women who did not consume iodine supplements (median=75µg/L, minimum-maximum 1-476 µg/L; p=0.003 Mann Whitney U test). Overall, there was an improvement in iodine status associated with the mandatory iodine fortification of bread. The median UIC of pregnant women not using a dietary supplement containing iodine during pregnancy was 68 µg/L (range 10-327 µg/L, n=84 samples) prior to bread fortification, and significantly increased to 84 µg/L (range 83.4- 393 µg/L, n=94 samples) post-intervention (p=0.01).
5. Table 2: The total n’s for each of the two columns should be included in the table, which I think should be 103 and 93, respectively. The percentages should be clarified overall for this table.

We apologise for this oversight. The correct n’s at each time point vary, and so have been added to the table to clarify what the percentages represent (see revised Table 2).